Optimal Design Theory in Early-Phase Dose-Finding Problems

by

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To my dearest mom and my cutest cat.

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The Sun —— Georg Trakl

Each day the gold sun comes over the hill.
The woods are beautiful, also the dark animals,
Also man hunter or farmer.

The fish rises with a red body in the green pond.
Under the arch of heaven,
The fisherman travels smoothly in his blue skiff.

The grain, the cluster of grapes, ripens slowly.
When the still day comes to an end,
Both evil and good have been prepared.

When the night has come,
Easily the pilgrim lifts his heavy eyelids;
The sun breaks from gloomy ravines.

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LIST OF ABBREVIATIONS

AE	Adverse event
AIC	Akaike information criterion
BCD	Biased-coin design
BIC	Bayesian information criterion
BOD	Biological optimal dose
CRM	Continual reassessment method
DA-CRM	Continual reassessment method coupled with data augmentation
DLT	Dose limiting toxicity
EM-CRM	Continual reassessment method coupled with EM algorithm
EWOC	Escalation with overdose control
GET	General equivalence theorem
OD-CRM	Continual reassessment method coupled with optimal design
OWEA	Optimal weight exchange algorithm
MED	Minimal effective dose
MLE	Maximum likelihood estimator
MTD	Maximum tolerated dose
RW	Random walk

LIST OF ABBREVIATIONS (Continued)

UaDR	Up-and-down rule
TER	Traditional escalation rule
TITE-CRM	Time-to-event continual reassessment method
sTER	Strict traditional escalation rule

SUMMARY

Phase I clinical trials concerns the estimation of the MTD (maximum tolerated dose), which is the dose level corresponding to the target toxicity rate p_t. If p_t is set to be 0.3, then it suggests that the on-going trial allows as many as 30% of the patients administered to the studying drug/compound to experience DLT (dose limiting toxicity). Once p_t is fixed, the MTD becomes the most crucial target to be identified, since it often serves as the upper bound for the dose range applied in the following phases of the study.

A great deal of methods have been proposed to address the MTD estimation problem, among which the CRM (continual reassessment method, (40)) stands out due to its simplicity and outstanding performance. The general idea behind CRM is that a dose-response curve would be assumed and fitted to the binary/Bernoulli toxicity data Y, and then each patient would be assigned to the dose that is most likely associated with the target toxicity rate, designated as the MTD. During the process, it treats the dose-toxicity curve as a function of x and p, where they represent dose level and toxicity probability, respectively. Then the function is solved for x, at the target toxicity rate p_t.

We extends the classic CRM by incorporating the idea of optimal design theory. More specifically, instead of assigning the most recent updated $\widehat{\text{MTD}}$ to the newly accrued cohort of patients, we build an optimal design on the latest estimated $\hat{\theta}$, where θ is the unknown parameter in the working model $\mathbf{E}(Y) = p = \psi(x, \theta)$. The resulting design, which guides the dose allocation for the newly recruited, would have the property of minimizing the asymptotic

variance of $\hat{\theta}$, which is formulated by using the Fisher information matrix of θ. We denote this new approach the OD-CRM, which indicates that this strategy is developed within the CRM framework, and coupled with the optimal design theory.

We employ the OD-CRM to identify the MTD under three working models, the simple power model, the two-parameter logistic model, and the two-parameter probit model, respectively. For simple power model, we prove that, regardless of the target toxicity rate specified in the trial, the OD-CRM always selects the dose level such that the corresponding toxicity rate is around 0.2, which is exactly the commonly used target toxicity rate. Moreover, through simulation studies done under varied scenarios, we show that by bringing in the idea of optimal design into the study, when the p_t is set beyond 0.2, the percentage of DLT occurrence will drop by a great amount. As for logistic and probit model, we prove that with the MTD being the target dose, the standard CRM approach would yield the exact optimal result, as produced by the OD-CRM, which justifies the efficiency of the CRM theoretically, from the perspective of optimal design theory.

Then we move on to a more practical problem encountered in oncology clinical studies, the late-onset toxicities. Due to the nature of the disease, some of the AEs (adverse event) would occur long after the initial drug administration, which brings great challenge to the early-phase dose-finding designs. To address this delayed-response issue, we adopt the weighting mechanism discussed in Cheung and Chappell (8), which essentially assigns each toxicity response to a weight that depends on the patient's enrollment time and the observed data. The weighted data are then incorporated into the working model to facilitate the following statistical inferences.

We continue the study for the same three models as mentioned above. For the simple power model, we draw a general conclusion regarding the optimal dose allocation at each stage of the trial because its parameter is a scalar which would make the resulting optimal designs universal and applicable to all different settings. As for the other two models, analytical results can only be obtained under a simplified setting where we only focus on D-optimality, and dose allocation for the first stage of the study (so there will be no existing designs from previous stages).

We also offer a general dose-finding algorithm, based on the OWEA (optimal weight exchange algorithm, (56)), to explore the performance of the OD-CRM under a broader clinical trial setup. We use the BMA (Bayesian model averaging) technique to unify all the three models in a weighted manner, and compare our method with three other widely applied ones, namely, the TITE-CRM (8), the EM-CRM (59), and the DA-CRM (32). Ours simulation results show the OD-CRM as a very promising novel approach in the sense that (a) its performance under various scenarios was stable even when the data were generated non-parametrically, (b) the percentages of correctly identifying the MTD it returned were the highest among all comparing methods, with the EM-CRM performing comparably to it, and (c) it tended to allocate most of the enrolled patients to the lowest two, three doses (with six in total), which would alleviate the safety and ethical concerns to a great extent.

Some possible future work are discussed in the end, which includes bringing in a different weighting mechanism, adding some randomness into the design, considering dose combinations, and involving efficacy data though the early phases.

CHAPTER 1

INTRODUCTION

Although the term "phase I" is sometimes applied to almost any early-phase trial, in clinical oncology studies, it usually refers specifically to a dose finding study where toxicity is the primary endpoint (13). For the agent being studied, the dose to be found here is the one with the greatest therapeutic effect and acceptable toxicity. We often refer to this dose as the MTD, i.e., maximum tolerated dose. It is served as the dose level upper bound for efficacy evaluation in the following Phase II study. The main focus of this thesis will be oncology phase I trials with a binary toxicity endpoint, with the goal of accurately identifying the MTD. [1]

1.1 MTD identification and methods proposed

Most designs for dose finding in phase I trials assume a nondecreasing dose-toxicity and dose-efficacy relationship. Under this assumption, highest dose indicates greatest therapeutic benefit; and if at the same time its toxic level is acceptable, then it is considered as the MTD, our research target.

To determine whether the toxic level of a certain dose is acceptable or not is not straightforward since patients' toxicity responses are heterogeneous. That is to say, at a given dose, some patients may experience little or no toxicity, while others show severe or fatal adverse symptoms. Therefore, acceptable toxicity is typically defined with respect to the percentage of

[1] Part of this Chapter was published in two of the author's publications (52) and (53).

toxicity occurrence in the whole population. For example, among a group of enrolled patients, after administration of a drug at a certain dose, 20% of them experience toxicity, then the toxic level of this dose is considered to be 0.2; and if the highest tolerable toxicity rate, or to say, the target toxicity rate is set to be 0.3, then this dose is viewed as safe/acceptable in terms of toxicity response.

The judgment of whether a patient experiences toxicity or not depends on the presence or absence of DLT, dose limiting toxicity. Suppose we grade all the expected adverse events (AEs) on a scale of 0 to 5, with each grade defined to be none, mild, moderate, severe, life-threatening, and fatal, then DLT can be deemed to be grade 3 or worse (standard in cancer: grade 4 hematologic or grade 3/4 non-hematologic toxicity). In this case, if in the trial a patient shows severe, i.e., grade 4, AEs, then he/she is presented with DLT, thus is recorded with 1 as the toxicity response.

Before moving on to specific approaches in identifying the MTD, we mention several design specifications. First, we do not consider treatment switch in the study due to possible cumulative effects from previous administered doses. Second, we assume doses given to the enrolled patients are chosen from a discrete candidate dose set $\mathcal{D} = \{d_1, ..., d_D\}$ designed before the trial begins, and issues like the choice of starting dose d_1, set size D, and dose spacing $d_j - d_i$, $1 \leq i < j \leq D$, are not the focus of this thesis thus are all considered pre-specified.

1.1.1 Non-parametric methods

In this subsection we briefly review some of the non-parametric methods proposed to identify the MTD in Phase I clinical trials. We start with the traditional escalation rule (TER, (48))

and its modification, the strict traditional escalation rule (sTER). Then the random walk (RW, (16)) strategies including the up-and-down rule (UaDR), the biased-coin design (BCD) are discussed.

1. TER and sTER

   The widely-applied TER is also known as the "3+3 design" where the decision of whether the current dose level d_i should decrease to d_{i-1}, stay the same, or increase to d_{i+1} depends on the cumulative toxicity responses recorded from all entered patients. More specifically, patients are treated in cohorts of three and are given the same dose level d_i. If none of them shows a DLT, the next cohort receives the next higher dose d_{i+1}; if two or more patients experience DLT, we de-escalate to level d_{i-1}; otherwise, the next cohort is treated at d_i again. Then if one out of six patients treated at d_i shows DLT, the trial goes up to d_{i+1}; otherwise, de-escalates to d_{i-1}. After that, few additional patients could be included to be treated at the stopping dose d_i, or its lower dose set $\{d_1, ..., d_{i-1}\}$. MTD is chosen to be the highest dose at which none or one out of six patients experiences DLT.

   If we want to put more awareness to the safety concern of an ongoing trial, the sTER provides a more conservative way of implementing the TER, in the sense that after the first cohort evaluation, if two or three patients show a DLT, the trial stops instead of decreasing to the next lowest level. In the end, the MTD can be identified as the highest dose level below the stopping dose, at which at least six patients have been treated with no more than one occurrence of DLT (additional patients may need to be recruited to meet this criterion). If no such dose exists, the starting dose d_1 would be taken as the

final estimation of the MTD. The typical "$3+3$ designs" can be generalized to the "$a+b$ designs" where $a+b=6$.

2. RW – UaDR and BCD

   The UaDR belong to the class of RWs since dose assignment of the next entered patient depends only on the toxicity response of the current patient, thus renders the dose allocation strategy to be a random walk which operates on the finite lattice of the given doses. The basic UaDR treats the newly-entered patient at the next lower dose d_{i-1} if the current patient exhibits DLT, otherwise he/she is given the next higher dose d_{i+1}. Several modifications have been proposed later to use UaDR as a tool in combining different designs.

   When combining with the $3+3$ rule, Storer later proposed several single-stage and two-stage UaD designs (see (48), (49), and (50)). Storer's C design (UaD-C) indicates that the trial proceeds following the UaDR and escalates only if two consecutive patients show no DLT. A slightly more advanced version is the Storer's D design (UaD-D) where three patients are treated at the same dose d_i. The trial escalates to d_{i+1} if no DLT is observed, and deescalates to d_{i-1} if more than one DLT occurs. Another cohort of three is treated at the same level d_i if only one patient out of the three shows a DLT. The two-stage design version of the above mentioned two approaches states that we implement the elementary UaDR until the first occurrence of DLT and the trial continues using the Storer's C design or the Storer's D design at the next lower dose level.

In addition to the UaDR, a BCD (15) also belongs to the category of sequential RW where the newly-entered patient is given the next lower dose d_{i-1} if a DLT is observed from the current enrolled patient who is treated at dose d_i; otherwise d_{i+1} is administered with probability $p \leq 0.5$, or d_i again with probability $1-p$. When boundary points d_1 or d_D is encountered, the algorithm stays at that dose level. It was shown that by choosing p to be $(p_t/1-p_t)$, with $p_t < 0.5$ being the target toxicity rate, the procedure will asymptotically center the allocation proportions unimodally around the MTD, the corresponding dose level of p_t.

1.1.2 Parametric methods

Due to the limitations of a small sample size and the lack of clinical information regarding the choice of MTD, non-parametric methods are argued to be less efficient compared with Bayesian methods in terms of accurate MTD estimation and economical study plan. In principle, Bayesian approaches allow one to combine available prior information with observed toxicity data to obtain a posterior MTD estimate that reflects pre-clinical knowledge and experiences, along with the updated information given by the patients enrolled in the ongoing trial.

The most applied Bayesian approach in identifying the MTD in Phase I clinical trials is the continual reassessment method (CRM, (40)). The procedure starts by assuming a working model ψ that depicts the monotone relationship between dose level x and its corresponding probability of DLT occurrence $\mathsf{P}(Y = 1|x, \theta)$, where Y is the binary toxicity response, and θ the unknown parameter. Thus we have $\mathsf{P}(Y = 1|\text{MTD}, \theta) = \psi(\text{MTD}, \theta) = p_t$, where p_t is the target toxicity rate.

A starting dose is given to the first cohort of patients using the prior estimation of the MTD, which is associated with the prior distribution of θ and the predetermined value of p_t. Then patients are brought into the study sequentially, with each cohort treated at the most recent estimated MTD calculated through θ update under Bayesian structure. If MTD estimate is not the same with any of the doses in the given candidate set, we choose the one that minimizes the distance between its estimated toxicity rate and p_t. In other words, the assumed dose-toxicity curve keeps being inverted to identify which one of the available levels has associated estimated toxicity probability as close as we can get to the targeted rate. After a fixed number of patients been evaluated fully, the final MTD estimate is the dose level that would be given to the hypothetical patient that enters next. More details regarding the CRM will be illustrated in Section 1.2.

Note that when the dimension of θ is one, like the simple power model, x in ψ dose not necessarily have to be the real dose level administered to patients; it can just be a dose label as long as the assumption of monotonicity is not violated. In this case it is required that for any x and p, there exists one and only one θ such that $\psi(x, \theta) = p$. The choice of this "dose label" mentioned above was discussed in detail in (9) using the word "skeleton" that represents one's prior belief regarding the toxicity rate associated with each does.

1.2 CRM and its practice with optimal design theory

Since its original introduction in 1990, the CRM often serve as a fundamental base for many subsequently proposed dose-finding approaches. It also provides us with an algorithm form for the key method described and established in this thesis, the OD-CRM, which combines optimal

design theory and the elementary structure of the CRM. Therefore, we feel it is necessary to elaborate more on this fundamental parametric dose-finding method, as well as its advantages and adjustments. Following that, we explain in short the reasons of developing a novel dose-finding method within the CRM framework, as well as the logic of incorporating optimal design theory into Phase I clinical trials.

1.2.1 Standard CRM procedure and related adjustments

We present the procedures for implementing the standard CRM as follows.

(I). Determine the target toxicity rate p_t and an available dose set $\mathcal{D} = \{d_1, ..., d_D\}$;

(II). Assume a working model $\psi(x, \theta)$ and a prior distribution $g_0(\theta)$ based on pre-clinical *in vitro* and *in vivo* studies;

(III). Assign dose $d_0^* \in \mathcal{D}$ to the first entered cohort where d_0^* minimizes either one of the following distance functions

i. $f_1(d) = d - \psi^{-1}(p_t, \hat{\theta}_0), \quad \hat{\theta}_0 = \int_\Omega \theta \cdot g_0(\theta) \mathrm{d}\theta$

ii. $f_2(d) = p_t - \int_\Omega \psi(d, \theta) \cdot g_0(\theta) \mathrm{d}\theta$

and Ω is the parameter space;

(IV). At step j, $j = 1, 2, ...$, we have $g_{j-1}(\theta)$ being the latest updated probability distribution of θ. We collect binary toxicity response Y_j from evaluated patients and assign dose $d_j^* \in \mathcal{D}$ to the $j + 1^{\text{th}}$ entered cohort where d_j^* minimizes either one of the following distance functions

i. $f_1(d) = d - \psi^{-1}(p_t, \hat{\theta}_j) \quad \hat{\theta}_j = \int_\Omega \theta \cdot g_{j-1}(\theta) \cdot L(\theta|Y_j)\mathrm{d}\theta$

ii. $f_2(d) = p_t - \int_\Omega \psi(d, \theta) \cdot g_{j-1}(\theta) L(\theta|Y_j)\mathrm{d}\theta$

and $L(\theta|Y_j)$ is the likelihood function;

(V). Repeat procedure (IV) until the accumulated sample size reaches a certain predetermined limit.

(VI). Final MTD estimate d^* is chosen from $\mathcal{D}$ that minimizes either one of the distance functions in (IV).

Remark 1. *Note that here j represents the last recruited cohort thus all estimates/distributions updates are final.*

Compared with some of the non-parametric methods where the next dose is based purely on the response of the current cohort, the CRM enjoys an advantage of making full use of all the available data at hand in order to give a better dose assignment. As indicated by Shen and O'Quigley (41), the CRM will converge eventually to the dose whose toxicity rate is closest to p_t, even when the working model is misspecified. Its practical performance under small to moderate samples, though, requires to be further investigated. Also, the CRM was shown to perform quite robustly in terms of dealing with the variation of the true θ value, in the sense that instead of trying to fit an overall model to the data obtained each time at a single chosen dose, which may cause problems like non-identifiability when parameter dimension is larger than one, the main goal of the CRM is rather to identify the target percentile, i.e., the MTD, from the assumed dose-toxicity curve.

Simulation study carried out by Korn et al. (29), Goodman et al. (21), and O'Quigley (38) all provided evidences of efficient operating characteristics of the CRM, in terms of a high percentage of accurately identifying the true MTD and a low rate of toxicity occurrence. When the prior used in the Bayesian structure is not too strong as to push the algorithm towards an aggressive direction, the CRM design behaves properly as well (9).

As for the safety issues that many investigators have doubt about, work done by O'Quigley and Chevret (39), O'Quigley and Shen (41), Ahn (1), Reiner et al. (43), O'Quigley (37) all indicated CRM to be safer than any of the commonly used up and down schemes when $p_t < 0.3$. It was also argued that CRM can easily be adjusted to increase its safety level simply by moving the target toxicity rate to a lower range, which in a way reinstates its flexibility advantage against most non-parametric designs.

Furthermore, extra flexibility can be gained by relaxing some of the model's rigidity. Instead of assuming a solo working model directly from the beginning, one could pick out a small finite set of candidate models and choose one that fits collected data the best under the heading of Bayesian model choice (20). Based on indifference intervals described by Cheung and Chappell (9), Lee and Cheung (30) provided procedures that can generate a satisfactory working model. The Bayesian model averaging (BMA) strategy adopted by Yuan and Yin (58) made use of the posterior estimates for the relevant toxic probabilities which are then weighted with respect to the corresponding posterior model probabilities.

Another parametric method that evolved from the CRM is the EWOC, i.e., escalation with overdose control (2). It shares the same framework as the CRM, with the main difference being

the dose assignment fashion at each enrollment time. The EWOC selects the next dose whose posterior probability exceeding the most recent updated MTD is equal to some pre-determined cutoff, for example, 0.25. Unlike the CRM, where each selected dose is the one closest to the current estimated MTD, the EWOC utilizes tolerance parameters to control the probability of aggressive dose escalation. After some stopping rule is being met, the final estimate of the MTD is calculated by minimizing the posterior expected loss with respect to a preset loss function. Model mis-specification within the context of overdose control was further investigated by Chu et al. (10). This is a very encouraging adaptation of the CRM when the ongoing trial has a primary concern of avoiding overdosing and models with higher parameter dimension are justified to be included in the study.

We should also mention that there is nothing particularly Bayesian about the CRM, whose basic framework can be adapted to a non-Bayesian setting where prior of θ is ignored and all parameter updates are entirely likelihood based. However, the working dose-toxicity model cannot be fit to the data until at least one patient shows DLT and another doesn't. Thus, additional guidance needs to be followed to lead the dose escalation process until heterogeneity is achieved. Two-stage designs were thus developed (see (48), (49), and (34)), where an "initial stage" was added to the algorithm which guarantees the heterogeneity in toxicity response in order to set off the likelihood-based estimation procedure. Practical modifications like involving additional patients or intermediate doses were also proposed later to meet some of the requirements in making Bayesian/frequentist inferences under certain model or parameter restrictions.

1.2.2 OD-CRM applied in general dose-finding problems

In the field of oncology product development, one needs to put extra effort on maintaining the balance between optimal dose before approval and rapid access to effective medications by patients (36). The possibility of recommending unacceptably toxic doses in traditional designs and the conservativeness of the standard CRM where a no-skipping rule is applied through the whole phase for most of the time make a revisit to early-phase dose finding methods urgently needed. FDA-AACR hosted an Oncology Dose Finding Workshop in June, 2016, where developing novel dose-fining strategies were highlighted and greatly encouraged.

It is pointed out that in reality, many non-optimal doses are taken into late-phase trials thus often resulting in a high rate of dose interruption. Given the recent emphasis put on obtaining better dose selections in early phases, the drive for conducting strictly rigorous dose-finding trials could be "dialed downed" a little. Moreover, the paradigm of determining a single dose, often the MTD, to investigate in Phase II studies requires to be altered in order to meet the more essential objective of Phase I designs, that is, recommendation of a safe and efficacious dose range based on which Phase II trials are to be conducted.

The necessity in speeding up drug development cannot be underestimated, especially in oncology trials due to the life-threatening nature of the disease. The single-dose allocation standard applied in all CRM-based methods may in some cases hinder the rapid-information-collection spirit. Also, the attention the CRM puts on one-point estimation (the MTD) helps in identifying the target quantile, but may show some weakness when establishing the dose-toxicity profile becomes a more crucial goal due to the increasing need in dose-ranging phase II trials.

In other words, MTD does not need to be estimated through all interim study time points; a slightly "diverged" path where more information on the underlying dose/response relationship is to be obtained may lead the way further into more efficient and conductive following phases. Finally, the battle between limited sample size and valid statistical inference has been addressed intensively in the early-phase studies. A design that can achieve a satisfying balance between the two is without doubt relevant and favorable.

It can be seen now that there exists enough reasons for us to bring in new aspects and ideas into early-phase dose-finding designs which can at the same time attend to the three issues stated in the last paragraph. Following this logic, we put forward a dose-finding technique where optimal design theory is incorporated into the basic CRM structure, i.e., the OD-CRM, where dose allocation at each interim time point is dealt with by creating optimal dose assignment. Such an approach can be expected to improve the dose selection process in the sense that (a) optimal dose assignments obtained at each step through constructing optimal designs are very likely to contain more than one doses, therefore proceeds the study by involving more patients into various doses in a timely fashion, allowing benefits and risks of the studied drug/compound to be understood earlier; (b) as compared to other CRM-based approaches where the estimated MTD is given to all patients in a single cohort, OD-CRM chooses dose(s) that is/are not directly related with the target toxicity rate but instead aiming at giving a better description of the dose-response relationship in the end; and (c) the underlying rationale of utilizing optimal design theory lies perfectly with the restrictions and goals in Phase I clinical trials, that is, to

increase statistical inference accuracy under a finite sample size, or to reduce the sample size given a specified estimation precision.

Suppose at an interim study point we recruit n patients and allocate them to the doses from the candidate dose set $\mathcal{D} = \{d_1, ..., d_D\}$, each with n_i observations, $i = 1, ..., D$. The purpose of optimal design here is to find a combination of $\{n_1, ..., n_D\}$ under restriction $\sum n_i = n$, such that the resulting design is the best with respect to some optimality criterion. Since such problem is in general intractable, the corresponding approximate designs, in which n_i's are replaced by their corresponding weights $\omega_i = n_i/n$, $i = 1, .., D$, are considered. A general approximate design can be expressed as follows,

$$\xi = \{(x_1, \omega_1), ..., (x_n, \omega_n)\}, \ \sum_{i=1}^{n} \omega_i = 1, \text{ and } x_i \in \mathcal{X}, \ i = 1, ..., n,$$

where we have n design points and $\mathcal{X}$ is the design space.

In order to identify optimal dose weights, one has to take into account the effect of those dose levels on the parameter estimation precision, which is generally reflected by the variance of the estimator. Based on Searle and Gruber (46), the variance-covariance matrix of the maximum likelihood estimator (MLE) of the parameter of interest, say $b(\theta)$, can be written as

$$\left(\frac{\partial b(\theta)}{\partial \theta}\right) \mathbf{I}^{-1}(\theta) \left(\frac{\partial b(\theta)}{\partial \theta}\right)^{T},$$

where $\mathbf{I}(\theta)$ is the Fisher information matrix of the model parameter.

On one hand, an optimal design aims at minimizing the variance-covariance matrix under some optimality criterion; on the other hand, the evaluation of Fisher information matrices for nonlinear models usually depend on the value of the unknown parameter. Thus, the challenge in designing an experiment under such situation is that while one is looking for the best design with the aim of better estimating the unknown parameter, one has to know the parameter value first to identify the best design. A common approach to tackle this dilemma is to use "locally" optimal designs, where we initiate the designing process based on a best "guess" of the unknown parameter (see (55) and (4)). This approach suits the sequential design framework in that the underlying model is refit once we have new observed outcomes and optimal design can be chosen based on the updated parameter value. Hereafter, the word "locally" is omitted for simplicity.

For a given design ξ, by standard asymptotic theory, the MLE of θ has approximately multivariate normal distribution with covariance matrix proportional to $\mathbf{I}_{\xi}^{-1}(\theta)$. We consider the MTD as a function of θ, i.e., $\text{MTD} = \psi^{-1}(x, \theta) := b(\theta)$, then the variance of the $\widehat{\text{MTD}} = b(\hat{\theta})$ under design ξ can be written as

$$\mathbf{V}_{\xi}(\widehat{\text{MTD}}) = \mathbf{V}_{\xi}(b(\hat{\theta})) = \left(\frac{\partial b(\theta)}{\partial \theta}\right) \mathbf{I}_{\xi}^{-1}(\theta) \left(\frac{\partial b(\theta)}{\partial \theta}\right)^{T} \Bigg|_{\theta=\hat{\theta}_{\xi}}. \tag{1.1}$$

A design ξ^* minimizing $\mathbf{V}(\widehat{\text{MTD}})$ results in an accurate estimation of the MTD, which can also be justified under the Bayesian framework: the asymptotic normal distribution of the $\widehat{\text{MTD}}$ approximates the posterior distribution of the $\widehat{\text{MTD}}$ under a Bayesian structure;

hence, minimizing the (log-) variance of the $\widehat{\text{MTD}}$ is equivalent to minimizing the (approximate) Shannon entropy of the posterior distribution of the $\widehat{\text{MTD}}$ (7).

1.3 Delayed-response problem

In some of the phase I settings dose escalation is based on toxicity responses recorded and evaluated within a relatively short period of time, typically no more than 4-6 weeks (13). It is expected to be the usual case where AEs associated with DLT appearance will occur soon after drug administration. However, there may be other scenarios where toxicities are undeveloped after the patient is brought into the study and start to take place after chronic dosing over an extended period of time. Any of the techniques mentioned earlier can be implemented without alteration in such a setting, where all previously-entered cohorts must be evaluated fully before another recruitment is permitted. One of the most dominant inferior consequences of that is the over-extended duration of the trial, some can even last for years.

On the other hand, if one tends to make use of all the data at hand from previously-entered cohorts without some weighting mechanism in operation, it is highly likely to give over-toxic dose recommendations in the end due to the use of short-term safety data and lack of accounting for intra-patient correlation between the early-showing and late-showing of DLT.

Unlike other general medicine which the targeting diseases are not as severe as cancer/tumor, drug development in oncology studies tends to have a higher tolerance on toxicity response if the drug shows promising efficacy. Thus, quicker identification of an efficacious dose can take precedence over finding an "absolute non-toxic" dose due to the special nature of the disease in study.

In real applications, especially within the oncology area, this delayed-response hurdle is quite regularly encountered. Here "response" can be referred as both the toxicity response and efficacy response; however, the majority of this thesis is focused on evaluating toxicity outcome only, the extended application of the method aiming at streamlining Phase I and II trials will be discussed in Chapter 5.

Here we breifly list some real clinical trials with late-onset toxicity presence. In radiotherapy trials, dose-limiting toxicities often occur long after the treatment is finished (see (11) and (12)). In a trial treating patients with pancreatic cancer, the full evaluation period was 9 weeks while the accrual rate was 1 per week (35). In the area of molecularly targeted agents, among a total of 445 patients in 36 trials, 57% of the grade 3 and 4 toxicities were late-onset (42). In a case study with gemcitabine-induced lung toxicity in breast cancer, the toxicity did not occur until more than a year after the initiation of gemcitabine therapy (47). Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program showed that Lymphoma treatment has evolved greatly to reflect the fact that even when cure is achieved, significant chronic or late-onset toxicity can vitiate long-term patient outcomes (24).

1.3.1 Methods proposed regarding the delayed-response problem

Relatively little attention has been paid to this study problem, one of the most early and noteworthy work being done in the field is the TITE-CRM (time-to-event CRM) design (see (8) and (5)). It has the same structure as that of the CRM, with the sole difference being the weight put on each observation when formulating the likelihood function. The standard CRM considers all responses as fully-evaluated, i.e., all with weight one; while the TITE-CRM

assigns weight w_i to the i^{th} observation based on its "reliability". A simple choice would be the ratio that patient's enrollment time u_i and the full evaluation period T which depends on the nature of the disease and curing drug/compound being studied. More complex versions of the weight functions were also discussed, most of which are related to the assumed distribution of the time-to-event variable for each patient/each dose level, or the instant risk at each time point. Both concepts are commonly seen in survival analysis.

In 2008, Bekele and colleges (3) modified the TITE-CRM framework by adding a set of rules with the goal to induce possibilities of enrollment suspension. The rules are established on the knowledge of the risk of toxicity at selected doses. If the predicted toxicity rate is deemed unacceptable, the design will temporarily suspend accrual until new data present evidence of a reduction on the predicted risk. In 2013, Wages, Conaway, and O'Quigley (54) explored the TITE-CRM design with the setting of dose combinations. The multiple-agent situation complicates the on-going trials due to the uncertainty with the dose-toxicity monotonicity, which could be reduced to a partial-order (PO) problem. Extension of the TITE-CRM to the PO setting was studied in the paper and was showed by simulation studies to be promising in the sense that it has similar performance in terms of the true MTD selection rate and a shorter trial duration at the same time.

Following work focused on this specific issue also adopted the thought of how to make use of all the "incomplete" observations. A natural thought would be treating them as missing data and utilizing existing strategies developed in the missing-data realm. Yuan and Yin in 2011 (59) proposed a method called the EM-CRM where censored observations due to incomplete follow-

ups are substituted in the parameter inference with expectations calculated using a modified EM algorithm. Later in 2013, Liu, Yin, and Yuan (32) proposed a similar method, the DA-CRM, where the Bayesian data augmentation technique was chosen to compensate for the incompleteness of the toxicity observations. Specifically, instead of deriving a posterior mean for each delayed response, a sample point is drawn from each posterior conditional distribution. Moreover, the model parameter is not estimated using the MLE as in the EM-CRM case, but again sampled from its corresponding posterior distribution.

We reviewed the following three methods in detail in chapter 2: the TITE-CRM, the EM-CRM, and the DA-CRM. In chapter 4, simulation studies are conducted to compare the performance of these designs with our proposed method, the OD-CRM in the late-onset toxicity setting, which will be introduced in the next section, and elaborated in chapter 3.

1.3.2 OD-CRM applied in the delayed-response problems

We assume for each enrolled patient, the entire evaluation time is T. Usually T is chosen by clinical investigators based on the disease nature and the treating mechanism to ensure that if a drug-induced DLT should occur, it would occur within the time interval $(0, T]$ after the administration of the treatment agent. There are K interim study intervals within each patient's evaluation period, namely, $(u_0, u_1]$, $(u_1, u_2]$,..., and $(u_{K-1}, u_K]$, where $u_0 = 0$ and $u_K = T$. Note that they do not have to be equally-spaced. For an enrolled patient, at time point $t = u_1, ..., u_{K-1}$, he/she may show late-onset toxicity; and by time u_K, he/she would have been fully evaluated, whether the response is toxicity or not. The trial will recruit new patients at each interim study time point, thus it is also the time for doing parameter inferences and

making dose allocation decisions. We also assume the independence between the recruitment and time-to-toxicity of patients.

As compared to Y_j, the true response of the j^{th} patient, we define here a new binary variable $Y_{j,k}$, $k = 1, ..., K$, as the toxicity outcome for patient j after being enrolled for time u_k, $k = 1, ..., K$. Note that when $k < K$, $Y_{j,k} = 1$ means toxicity response has been observed, i.e., $Y_j = 1$; but $Y_{j,k} = 0$ doesn't necessarily mean that there's no DLT, it only says that the true response Y_j is still missing/waiting to be observed till time u_K.

- If $Y_{j,k} = 1$, for $k = 1, ..., K$, then $Y_j = 1$, and patient j is considered fully-evaluated with DLT;
- If $Y_{j,K} = 0$, then $Y_j = 0$, and patient j is considered fully-evaluated without DLT;
- If $Y_{j,k} = 0$, for $k = 1, ..., K-1$, then Y_j is missing, and patient j is considered not fully-evaluated with late-onset toxicity.

Notice that the missing data mechanism being discussed here is not at random in the sense that its missing nature depends on the time-to-toxicity of patients under given agent(s) thus should be considered informative and non-disregardable. It is also a special case of non-ignorable missing data since the missing mechanism can be defined as follows,

$$M_j(U_j) = \begin{cases} 1 & \text{if } U_j > t \text{ and } t < T, \\ 0 & \text{if } U_j \leq t \leq T \text{ or } U_j = \infty, \end{cases}$$

where t is the actual follow-up time, and $M_j(U_j)$ and U_j denote the missing data indicator and time-to-toxicity of patient j, respectively. Note that $U_j = \infty$ means no DLT before T.

We adopt the idea of bringing a weight function w that depicts the relationship between true response $Y_\cdot$ and the interim outcome $Y_{\cdot,k}$ (8). This weight function in the form of a vector with each dimension contributing to each interim time point, $w = (w_1, ..., w_K)$, can be seen as conditional probabilities such that given the fact that patient will show DLT by the end of the evaluation period, what is the probability that he/she will show DLT by time u_k, $k = 1, ..., K$. Thus for patient j, we have

$$\begin{aligned} w_k &= \mathsf{P}(\text{Tox by time } t_k | \text{Tox by the end}) \\ &= \mathsf{P}(Y_{j,k} = 1 | Y_j = 1), \end{aligned}$$

and model $Y_{j,k}$ can thus be given as

$$\begin{aligned} \mathsf{P}(Y_{j,k} = 1) &= w_k \psi(x_j, \theta), \\ \mathsf{P}(Y_{j,k} = 0) &= 1 - w_k \psi(x_j, \theta), \end{aligned}$$

where as stated in Section 1.1.3, ψ is the working model and x_j the dose level of patient j.

We can see that pseudo data $Y_{\cdot,k}$'s are thus included in the design in a "down-weighted" manner. In summary, the joint probabilities of outcomes for patient j by time u_k, $k = 1, ..., K-1$, i.e., $Y_{j,k}$'s, and time $u_K = T$, i.e., Y_j, are presented in Table 1.

	Pseudo response by time u_k		Row total
True response by time T	No-DLT ($Y_{j,k}=0$)	DLT ($Y_{j,k}=1$)	
No-DLT ($Y_j=0$)	$1-\psi(x_j,\theta)$	0	$1-\psi(x_j,\theta)$
DLT ($Y_j=1$)	$(1-w_k)\psi(x_j,\theta)$	$w_k\psi(x_j,\theta)$	$\psi(x_j,\theta)$
Column total	$1-w_k\psi(x_j,\theta)$	$w_k\psi(x_j,\theta)$	1

Table 1: Joint probabilities of outcomes by time u_k and $u_K = T$ for patient j

We can see that the row totals correspond to the Bernoulli distribution of Y_j, and the column totals yield the marginal distribution of $Y_{j,k}$, $k = 1, ..., K$.

For patient j who hasn't shown DLT by time u_{k-1}, i.e., $Y_{j,k-1} = 0$, we define two conditional probabilities, $\tilde{p}_{j,k}$, $\tilde{q}_{j,k}$, to depict his/her random toxicity outcome by the next time point u_k:

$$\begin{aligned}\tilde{q}_{j,k} &= \mathsf{P}(Y_{j,k}=0|Y_{j,k-1}=0) = \frac{\mathsf{P}(Y_{j,k}=0, Y_{j,k-1}=0)}{\mathsf{P}(Y_{j,k-1}=0)} \\ &= \frac{\mathsf{P}(Y_{j,k}=0)}{\mathsf{P}(Y_{j,k-1}=0)} = \frac{1-w_k\psi(x_j,\theta)}{1-w_{k-1}\psi(x_j,\theta)}, \qquad (1.2)\end{aligned}$$

$$\begin{aligned}\tilde{p}_{j,k} &= \mathsf{P}(Y_{j,k}=1|Y_{j,k-1}=0) = 1-\mathsf{P}(Y_{j,k}=0|Y_{j,k-1}=0) \\ &= 1-\frac{1-w_k\psi(x_j,\theta)}{1-w_{k-1}\psi(x_j,\theta)} = \frac{(w_k-w_{k-1})\psi(x_j,\theta)}{1-w_{k-1}\psi(x_j,\theta)}. \qquad (1.3)\end{aligned}$$

Note that $\tilde{p}_{j,k} + \tilde{q}_{j,k} = 1$.

Now with the marginal and conditional probabilities defined above, for the sake of illustration hereafter, we define two joint probabilities

$$q_{j,k} = \mathsf{P}(Y_{j,k} = 0, Y_{j,k-1} = 0) = \mathsf{P}(Y_{j,k} = 0) = 1 - w_k\psi(x_j, \theta), \tag{1.4}$$

$$p_{j,k} = \mathsf{P}(Y_{j,k} = 1, Y_{j,k-1} = 0) = \mathsf{P}(Y_{j,k} = 1|Y_{j,k-1} = 0) \cdot \mathsf{P}(Y_{j,k-1} = 0) = (w_k - w_{k-1})\psi(x_j, \theta). \tag{1.5}$$

Note that $p_{j,k} + q_{j,k} = \mathsf{P}(Y_{j,k-1} = 0) = q_{j,k-1}$.

To summarize and compare, we have all defined (conditional/marginal/joint) probabilities (for patient j) tabulated as follows.

Marginal	$q_{j,k} = \mathsf{P}(Y_{j,k} = 0) = 1 - w_k\psi(x_j, \theta)$
Conditional	$\tilde{p}_{j,k} = \mathsf{P}(Y_{j,k} = 1\|Y_{j,k-1} = 0) = \dfrac{(w_k - w_{k-1})\psi(x_j, \theta)}{(1 - w_{k-1})\psi(x_j, \theta)}$
	$\tilde{q}_{j,k} = \mathsf{P}(Y_{j,k} = 0\|Y_{j,k-1} = 0) = \dfrac{1 - w_k\psi(x_j, \theta)}{1 - w_{k-1}\psi(x_j, \theta)}$
Joint	$p_{j,k} = \mathsf{P}(Y_{j,k} = 1, Y_{j,k-1} = 0) = (w_k - w_{k-1})\psi(x_j, \theta)$
	$q_{j,k} = \mathsf{P}(Y_{j,k} = 0, Y_{j,k-1} = 0) = \mathsf{P}(Y_{j,k} = 0) = 1 - w_k\psi(x_j, \theta)$
Relation	$\tilde{p}_{j,k} \cdot q_{j,k-1} = p_{j,k}$
	$\tilde{q}_{j,k} \cdot q_{j,k-1} = q_{j,k}$

Table 2: Probabilities of different events for patient j

The design problem here is to find an optimal dose allocation $\xi = \{(d_i, \omega_i), i = 1, ..., D\}$ for each recruitment, at the beginning of the experiment. Specifically, suppose now we are at a certain time point t, and we are to make inferences based on the data collected by time t, i.e., to obtain $\hat{\theta}|$(data by time t). In order to obtain the most efficient $\hat{\theta}$, we need to guarantee data collected by then are informative, which requires us to optimize the "information" we are to obtain by time t.

As stated in Section 1.2.3, the construction of ξ depends on the minimization of the asymptotic variance of $\widehat{\text{MTD}}$ (Equation 1.1), which we can see is not influenced by data collected along the way, i.e., independent of data Y. Thus optimal designs/dose allocations for each recruitment are constructed at the beginning of the trial, rather than at each study time point. We should mention that since locally optimal designs are dependent on the value of parameter θ, which keeps updating at each stage, thus the designs constructed are "unchanged" in terms of their corresponding "formulas", instead of the actual values of each design point and weight, with which the dose allocations are guided.

CHAPTER 2

PREVIOUS WORK ON DELAYED-RESPONSE

Since MTD is defined in a DLT percentile manner with respect to a fixed duration of time, and is usually assumed to be less than the time of patient enrollment in a trial, then when there are long-term toxicities present, it is very likely that the trial will overestimate the MTD due to the mistreating of the late-onset toxicities as no-DLTs. Numerous examples that have been given in Section 1.3.1 showed that an increasing need in new methods tackling the delayed-response problem, which is also considered a major drawback of the original CRM where its timeliness was seriously criticized. In this chapter we summarize and compare several methods that are proposed in the context of late-onset toxicities, including their setups and methodologies.

2.1 TITE-CRM

In 2000, Cheung and Chappell (8) proposed a method that incorporates the time-to-event of each patient into the CRM, denoted as the TITE-CRM, which allows patients to be entered in a staggered fashion. By defining a weight function which builds a bridge between the observed data at each interim study time point and the true toxicity responses in the end, the TITE-CRM is essentially an extension of the original CRM which occurs under the situation that all enrolled patients being censored by the end of the evaluation period T.

More specifically, the TITE-CRM extends CRM by considering a weighted dose-response model $G(d, w, \theta)$ that is monotone increasing in w with marginal constraints

$$G(d, 0, \theta) = 0,$$

and

$$G(d, 1, \theta) = \psi(d, \theta),$$

where d is the dose and $\psi(d, \theta)$ the dose-response model in a standard CRM setup. Therefore, θ is estimated based on the weighted likelihood

$$L_n(\theta) = \prod_{i=1}^{n} G(d_{[i]}, w_{i,n}, \theta)^{y_{i,n}} (1 - G(d_{[i]}, w_{i,n}, \theta))^{1-y_{i,n}} \tag{2.1}$$

where $y_{i,n}$ and $w_{i,n}$ are, respectively, the indication of toxic response for the i^{th} patient and the weight assigned to this observation before the $(n+1)^{\text{th}}$ patient enters. Motivated by simplicity and the goal of satisfying the marginal constraints, here the paper proposed to incorporate w linearly into ψ. That is,

$$G(d, w, \theta) = w\,\psi(d, \theta) \text{ for } w \in [0, 1]. \tag{2.2}$$

Similar to the classic CRM setup, it follows that the weighted likelihood L_n defined in Equation 2.1 is a regular likelihood if G is the assumed model. In fact, model G (Equation 2.2)

can be viewed as a time-to-toxicity regression model. Let U_i be the time-to-toxicity for patient i, then we have

$$\begin{aligned} G(d_{[i]}, w_i, \theta) &= H_i(u) \qquad \text{(cdf of the random variable } U_i\text{)} \\ &= \mathsf{P}(U_i \le u) \\ &= \mathsf{P}(U_i \le u | U_i \le T)\mathsf{P}(U_i \le T) + \mathsf{P}(U_i \le u | U_i \ge T)\mathsf{P}(U_i \ge T) \\ &\overset{\mathsf{P}(U_i \le u | U_i \ge T)=0}{=\!=\!=\!=\!=\!=\!=\!=\!=\!=\!=} \mathsf{P}(U_i \le u | U_i \le T)\mathsf{P}(Y_i = 1) \\ &\overset{set}{=} w_i(u, T)\psi(d_{[i]}, \theta). \end{aligned} \tag{2.3}$$

Thus the weight function w_i is identified with a truncated probability distribution of U_i with $w_i(0, T) = \mathsf{P}(U_i \le 0 | U_i \le T) = 0$ and $w_i(T, T) = \mathsf{P}(U_i \le T | U_i \le T) = 1$; and the dose-response curve ψ with the marginal model at time T. Notice here the regression interpretation justifies the linearly-incorporated weight model stated in Equation 2.2. We could see that although the subscript i in U_i and $H_i(u)$ indicates different patients, the real influence factor is the dose assigned to that patient $d_{[i]}$; thus hereafter we refer time-to-toxicity U_i and its cdf $H_i(u)$ not by each patient, but by each corresponding dose level, $d_i \in \mathcal{D}$, where $\mathcal{D}$ is the dose set.

During the implementation of the TITE-CRM method in a trial, according to the regression model (Equation 2.3), we present three cases here to involve all possible outcomes that are to be observed.

- When $Y_i = 1$, i.e., a DLT is observed, full information from this patient should be claimed by setting w_i to 1. This is also justified by the definition of w_i above, which is $\mathsf{P}(U_i \le$

$u|U_i \leq T$) taking value 1 since DLT is already observed at this point which would make the patient's time-to-toxicity U_i fall before this time point u. Therefore, contribution of observation $Y_i = 1$ to the weighted likelihood (Equation 2.1) is

$$G(d_{[i]}, w_i, \theta)^{Y_i}(1 - G(d_{[i]}, w_i, \theta))^{1-Y_i}$$
$$= G(d_{[i]}, w_i, \theta) = w_i\, \psi(d_{[i]}, \theta) = \psi(d_{[i]}, \theta).$$

- When $Y_i = 0$ and the patient's follow-up time u_i is less than T, contribution of observation $Y_i = 0$ to the weighted likelihood (Equation 2.1) is

$$G(d_{[i]}, w_i, \theta)^{Y_i}(1 - G(d_{[i]}, w_i, \theta))^{1-Y_i}$$
$$= 1 - G(d_{[i]}, w_i, \theta) = 1 - w_i(u_i, T)\psi(d_{[i]}, \theta).$$

- When $Y_i = 0$ and the patient's follow-up time u_i reaches T, contribution of observation $Y_i = 0$ to the weighted likelihood (Equation 2.1) is

$$G(d_{[i]}, w_i, \theta)^{Y_i}(1 - G(d_{[i]}, w_i, \theta))^{1-Y_i}$$
$$= 1 - G(d_{[i]}, w_i, \theta) = 1 - w_i(u_i, T)\psi(d_{[i]}, \theta)$$
$$= 1 - w_i(T, T)\psi(d_{[i]}, \theta) = 1 - \psi(d_{[i]}, \theta).$$

Two patient-homogeneous weight functions were discussed by the authors. The first would bring the weight function under an accelerated failure time model as

$$w(u;T,d,\theta)=\frac{\psi_0\{\log(u/T)^c-a+\theta d\}}{\psi_0\{\theta(d-a/\theta)\}},$$

where ψ_0 is some distribution and model parameter $\theta>0$. This weight function has the advantage of being sensitive to data and could reevaluate w_i's adaptively according to the toxicity observations recorded through the trial.

Another weight scheme that does not depend on the model parameter was introduced as

$$w(u;T)=\frac{\mathfrak{k}}{z+1}+\frac{1}{z}\left(\frac{u-t_{(\mathfrak{k})}}{t_{(\mathfrak{k}+1)}-t_{(\mathfrak{k})}}\right),$$

where z is the total number of toxic observations, $0=t_{(0)}<t_{(1)}\leq\cdots\leq t_{(z)}<t_{(z+1)}=T$ are the ordered failure times, and $\mathfrak{k}=\max_{0\leq j<z}\{j:u\geq t_{(j)}\}$. This weight function puts less weight on each observed Y if DLTs have been recored at the second half of the evaluation period, and even less weight on newly-enrolled patients when some toxic data are observed near the end, i.e., when u is close to T.

In this paper, the weight function was taken to be the ratio of the actual follow-up time u to the entire evaluation period T, i.e.,

$$w(u,T)=\frac{u}{T}, \tag{2.4}$$

which is patient-homogeneous and independent of the toxicity observations. It might be considered as oversimplified, yet, according to the authors, has been shown to be sufficient under many design scenarios.

Due to the limitations when using the MLE before the appearance of DLTs under the frequentist paradigm, and the possible over-aggressive escalation with an informative prior under the Bayesian structure, an initial design which determines an early-stage dose escalating scheme together with a transition rule that helps move design to the proposed model-based TITE-CRM stage, was implemented in the simulation studies. More specifically, three patients are included at a time starting at the lowest dose, and the design will level up to the next dose given no reported DLTs. The switch to the TITE-CRM happens after the first occurrence of a toxicity response. It was also the initial design considered in O'Quigley and Shen (41).

In implementing the TITE-CRM, the dose-response model ψ was chosen to be $\psi(\alpha) = p_d^{\alpha}$, and the prior distribution on the model parameter α was taken to be $g(\alpha) = 1 - \exp(-\alpha)$ for $\alpha > 0$. There were six doses involved, with prior belief/skeleton set to be $(p_1, p_2, p_3, p_4, p_5, p_6) = (0.05, 0.10, 0.20, 0.30, 0.50, 0.70)$. Five toxicity configurations used in O'Quigley et al. (40) were used in the simulation. See Table 3.

The TITE-CRM algorithm can then be described as follows,

(I). If the initial stage is not implemented, then we start the trial by treating the first cohort at the *a priori* best dose determined by parameter prior $g(\alpha)$. Otherwise, we begin with the initial stage where the first entered cohort is treated at the lowest dose and fully

Toxicity probability
0.05, 0.10, 0.20, 0.30, 0.50, 0.70
0.30, 0.40, 0.52, 0.61, 0.76, 0.87
0.05, 0.06, 0.08, 0.11, 0.19, 0.34
0.06, 0.08, 0.12, 0.18, 0.40, 0.71
0.00, 0.00, 0.03, 0.05, 0.11, 0.22

Table 3: Toxicity configurations in the TITE-CRM simulation

followed; dose is escalated continuously until the appearance of the first DLT. Then we switch to the TITE-CRM.

(II). At the current stage, α is estimated following the regression model (Equation 2.3) with weight function $w = u/T$ and working model $\psi = p_d^{\alpha}$. The parameter inference can be handled either under the Bayesian framework, i.e., the posterior mean, or follow the frequentist manner, i.e., the MLE. Then the dose allocation for the next cohort is the one with toxicity probability closest to p_t, the target toxicity rate.

(III). Once the pre-determined maximum sample size is reached, based on the final estimate of model parameter α, the dose that has the toxicity probability closest to p_t is selected as the MTD.

2.2 EM-CRM

In 2011, Yuan and Yin (59) proposed a method targeting the late-onset toxicity problem that treats unobserved toxicity outcomes as missing data, or to say, censored observations due

to incomplete follow ups, and then utilizes a modified EM algorithm (14) as the main technique to adjust the standard CRM design, denoted as the EM-CRM.

Again, let U_i denote time-to-toxicity of each patient, and u_i the actual follow-up time. It then follows that

$$Y_i = \begin{cases} 1 & \text{if } U_i \leq u_i \leq T \\ 0 & \text{if } U_i > u_i = T \\ \text{missing} & \text{if } U_i > u_i, \text{ and } u_i < T \end{cases} \tag{2.5}$$

where T is the entire evaluation period. Note that U_i is considered as a continuous random variable. Under the case when $Y_i = 0$, we set $U_i = \infty$; otherwise, U_i takes value in $(0, T]$.

Some notation used in the paper which have bot been introduced before are now listed here with slight modifications in order to be consistent with the following sections.

- $u_0 < u_1 < \cdots < u_K$: distinct observed event times with $u_0 = 0$ and $u_K = T$.
- m_k: number of DLTs occurred at u_k for $k = 0, ..., K-1$.
- c_k: number of censored observations in the interval $[u_{k-1}, u_k)$ for $k = 1, ..., K$.
- $\mathcal{C}_k$: set of censored observations in the interval $[u_{k-1}, u_k)$ for $k = 1, ..., K$.
- $\boldsymbol{\lambda} = (\lambda_0, ..., \lambda_{K-1})$: unknown discrete hazards at $u_k's$ with $\lambda_k = \mathsf{P}(U = u_k | U \geq u_k)$ and $1 - \lambda_k = \mathsf{P}(U > u_k | U \geq u_k)$.

Under CRM-based designs, the log-likelihood of the complete data is a linear function of the i^{th} response Y_i, $i = 1, 2, ..., n$. Assuming simple power model $\psi_d(\alpha) = p_d^{\exp(\alpha)}$, $d = 1, ..., D$,

as the working model, when applying the EM algorithm, at the r^{th} iteration, given the current parameter estimates $\alpha^{(r)}$ (parameter in the dose-response model) and $\boldsymbol{\lambda}^{(r)}$ (discrete hazards at each observed event time points), the E step of the $(r+1)^{\text{th}}$ iteration essentially substitutes the missing value of y_i directly with its expectation in the form of

$$
\begin{aligned}
&E(Y_i^{(r+1)}|U_i > u_i, \alpha^{(r)}, \boldsymbol{\lambda}^{(r)}) \\
&= \mathsf{P}(Y_i^{(r+1)} = 1|U_i > u_i, \alpha^{(r)}, \boldsymbol{\lambda}^{(r)}) \\
&= \frac{\mathsf{P}(Y_i^{(r+1)} = 1|\alpha^{(r)})\mathsf{P}(U_i > u_i|Y_i^{(r+1)} = 1, \boldsymbol{\lambda}^{(r)})}{\mathsf{P}(Y_i^{(r+1)} = 1|\alpha^{(r)})\mathsf{P}(U_i > u_i|Y_i^{(r+1)} = 1, \boldsymbol{\lambda}^{(r)}) + \mathsf{P}(Y_i^{(r+1)} = 0|\alpha^{(r)})\mathsf{P}(U_i > u_i|Y_i^{(r+1)} = 0, \boldsymbol{\lambda}^{(r)})} \\
&= \frac{\psi(d_i, \alpha^{(r)}) \prod_{k:u_k<u_i}(1-\lambda_k^{(r)})}{\psi(d_i, \alpha^{(r)}) \prod_{k:u_k<u_i}(1-\lambda_k^{(r)}) + 1 - \psi(d_i, \alpha^{(r)})}. \qquad (2.6)
\end{aligned}
$$

Note that the second equality comes from the the probability law that

$$\mathsf{P}(A|B) = \frac{\mathsf{P}(A)\mathsf{P}(B|A)}{\mathsf{P}(A)\mathsf{P}(B|A) + \mathsf{P}(A^c)\mathsf{P}(B|A^c)},$$

and the last equality stems from the fact that

$$\mathsf{P}(U_i > u_i|Y_i^{(r+1)} = 0, \boldsymbol{\lambda}^{(r)}) = \mathsf{P}(U_i > u_i|U_i = \infty) = 1,$$

and

$$\mathsf{P}(U_i > u_i|Y_i^{(r+1)} = 1, \boldsymbol{\lambda}^{(r)}) = \prod_{k:u_k<u_i}(1-\lambda_k^{(r)}).$$

Then in the following M-step, the likelihood function

$$L(\alpha|\mathbf{y}) = \prod_{i=1}^{n} \left\{ p_{d_i}^{\exp(\alpha)} \right\}^{y_i} \left\{ 1 - p_{d_i}^{\exp(\alpha)} \right\}^{1-y_i} \tag{2.7}$$

is updated by substituting y_i with $y_i^{(r+1)}$, where depending on Equation 2.5, $y_i^{(r+1)}$ is either 1, 0, or $E(Y_i^{(r+1)})$ obtained in Equation 2.6. It can be shown that

$$\lambda_k^{(r+1)} = \frac{m_k}{\sum_{j=k}^{K-1} \left(m_j + \sum_{i \in \mathcal{C}_j} y_i^{(r+1)} \right)}, \quad k = 0, 1, ..., K-1,$$

is analogous to the Kaplan-Meier estimator (27); and $\alpha^{(r+1)}$ is obtained through maximizing the updated likelihood function $L(\alpha|\mathbf{y}^{(r+1)})$ (Equation 2.7).

To enhance the robustness of the design, S sets of toxicity probabilities/skeletons, namely, $\{p_{11}, ..., p_{1D}\}$,..., $\{p_{S1}, ..., p_{SD}\}$, each leading to an independent CRM power model, were proposed to be specified simultaneously. Frequentist approaches, which avoid specifying prior distributions, are adopted in the following algorithm. More specifically, two methods are selected to evaluate the importance of each model.

- Model selection

  Two commonly applied information criteria, AIC and BIC, are both considered. Since in this case, for each candidate model, r, the number of model parameters, and n, the number of observations are the same, these two criteria are equivalent. Essentially, the model selected in each step is the one with the largest likelihood value (Equation 2.7).

- Model averaging

  Compared with model selection where inferences and dose escalations ad de-escalations are based solely on one chosen model, model averaging method is considered to be more robust in the sense that it can account for additional uncertainty brought in by the variability in the candidate model set where the ambiguity of the working model gets acknowledged and following inferences are standing on all the competing models instead of a single chosen one.

  The smoothed AIC estimator (see (6) and (23)) is used as the estimate of the toxicity probability across all candidate models. That is,

$$\bar{\psi}_d = \sum_{s=1}^{S} w_s \, \hat{\psi}_{sd} = \sum_{s=1}^{S} w_s \, \psi_{sd}^{\exp(\hat{\alpha}_s)}, \tag{2.8}$$

  where $\hat{\alpha}_s$ is the MLE of α_s obtained through the EM algorithm under the s^{th} model, and

$$w_s = \frac{\exp(-\text{AIC}_s/2)}{\sum_{s=1}^{S} \exp(-\text{AIC}_s/2)}$$

  with $\text{AIC}_s = -2 \log L_s + 2r$ for $s = 1, ..., S$.

In implementing the EM-CRM, six dose levels constituted the dose set $\mathcal{D}$ with monotonously increasing toxicity probabilities. A total of eight toxicity scenarios were assumed and listed in

Table 4. Three skeletons were used to represent three different power models with their own prior opinions:

$$(p_1, p_2, p_3, p_4, p_5, p_6) = \begin{cases} (0.05, 0.14, 0.18, 0.22, 0.26, 0.30), \text{ skeleton 1} \\ (0.08, 0.12, 0.20, 0.30, 0.40, 0.50), \text{ skeleton 2} \\ (0.20, 0.30, 0.40, 0.50, 0.60, 0.70), \text{ skeleton 3} \end{cases}$$

Toxicity scenarios
0.08, 0.10, 0.12, 0.30, 0.50, 0.60
0.06, 0.08, 0.10, 0.15, 0.30, 0.45
0.05 0.14, 0.18, 0.22, 0.26, 0.30
0.20, 0.30, 0.40, 0.50, 0.60, 0.70
0.08, 0.12, 0.20, 0.30, 0.40, 0.50
0.05, 0.10, 0.30, 0.50, 0.60, 0.70
0.02, 0.03, 0.04, 0.05, 0.30, 0.50
0.50, 0.60 ,0.70, 0.80, 0.85, 0.90

Table 4: Toxicity configurations in the EM-CRM simulation

Suppose patients are treated in cohorts. For safety, dose escalation and de-escalation are restricted by one dose level at a time. The EM-CRM algorithm can then be described as follows,

(I). The first entered cohort is treated at the lowest dose and fully followed; dose is escalated continuously until the appearance of the first DLT. Then we switch to EM-CRM.

(II). At the current dose level d^{curr}, based on the cumulated data, we obtain the estimates for the toxicity probabilities, $\bar{\psi}_d$, $d = 1, ..., D$, using the EM-algorithm coupled with model selection or model averaging procedure. Then we find d^* such that

$$d^* = \text{argmin}_{d \in \mathcal{D} = \{1,..,D\}} \left| \bar{\psi}_d - p_t \right|.$$

Then

- if $d^{curr} > d^*$, the next dose level will decrease to $d^{curr} - 1$;
- if $d^{curr} < d^*$, the next dose level will increase to $d^{curr} + 1$;
- if $d^{curr} = d^*$, the next dose level will remain at d^{curr}.

(III). Once the maximum sample size is reached, the dose that has the toxicity probability closest to p_t is selected as the MTD.

2.3 DA-CRM

In 2013, Liu, Yin, and Yuan (32) proposed another method targeting the late-onset toxicity problem where incomplete toxicity outcomes are also treated as missing data, as in the EM-CRM design. The difference of the two methods lies in the substitution of the incomplete observations. Instead of calculating an expectation of each pseudo data point, the DA-CRM design adopts the Bayesian data augmentation strategy (51) to sample both the missing responses and model

parameters from their corresponding posterior full conditional distributions. The method was denoted as the DA-CRM where DA stands for data augmentation.

The setup here is very similar to the one stated under the EM-CRM method, so we will not describe again. We also use the notation introduced in Section 2.2.1 with two additional ones:

- $x_i = \min(U_i, u_i)$: the observed time, where U_i still denote the time-to-toxicity of patient i, and u_i his/her actual follow-up time.
- δ_{ik}: toxicity indicator of patient i in the k^{th} time interval $[u_{k-1}, u_k)$, $k = 1, ..., K$.

Again assuming simple power model $\psi_d(\alpha) = p_d^{\exp(\alpha)}$, $d = 1, ..., D$, as the working model with prior $\alpha \sim \text{N}(0, \sigma^2)$, when applying the DA algorithm, at the r^{th} iteration, given the current parameter estimates $\alpha^{(r)}$ and $\boldsymbol{\lambda}^{(r)}$, the I (imputation) step of the $(r+1)^{\text{th}}$ iteration essentially samples the missing value of y_i from its full conditional distribution given by

$$Y_i^{(r+1)} | (\alpha^{(r)}, \boldsymbol{\lambda}^{(r)}) \sim \text{Ber}\left(\frac{\psi(d_i, \alpha^{(r)}) \exp\left(-\sum_{k=0}^{K-1} \lambda_k^{(r)} s_{ik} \right)}{\psi(d_i, \alpha^{(r)}) \exp\left(-\sum_{k=0}^{K-1} \lambda_k^{(r)} s_{ik} \right) + 1 - \psi(d_i, \alpha^{(r)})} \right), \tag{2.9}$$

where $s_{ik} = u_k - u_{k-1}$ if $x_i > u_k$, $s_{ik} = x_i - u_{k-1}$ if $x_i \in [u_{k-1}, u_k)$, and $s_{ik} = 0$ otherwise.

Then in the following P (posterior) step, observed data $\mathbf{y}^{(r)} = (y_1^{(r)}, ..., y_n^{(r)})$ is updated by substituting $y_i^{(r)}$ with $y_i^{(r+1)}$, where still depending on Equation 2.5, $y_i^{(r+1)}$ is either 1, 0, or the imputed data sampled according to Equation 2.9, respectively. Then $\alpha^{(r+1)}$ is sampled from its posterior distribution

$$f(\alpha | \mathbf{y}^{(r+1)}) \propto L(\alpha | \mathbf{y}^{(r)}) \cdot g(\alpha)$$

where $L(\alpha|\mathbf{y})$ is the likelihood under simple power model (Equation 2.7) and $g(\alpha)$ the density function of $\mathrm{N}(0, \sigma^2)$. Similarly, $\boldsymbol{\lambda}^{(r+1)}$ is then sampled from its posterior

$$\lambda_k^{(r+1)}|\mathbf{y}^{(r+1)} \sim \text{Gamma}\left(\frac{\tilde{\lambda}_k}{2} + \sum_{i=1}^{n} \delta_{ik}, \frac{1}{2} + \sum_{i=1}^{n} y_i^{(r+1)} s_{ik}\right),$$

where $\tilde{\lambda}_k = \dfrac{K}{T(K-k+0.5)}$, for $k = 0, 1, ..., K-1$.

Toxicity scenarios
0.10, 0.15, 0.30, 0.45, 0.60, 0.70
0.08, 0.10, 0.20, 0.30, 0.45, 0.60
0.15, 0.30, 0.45, 0.60, 0.70, 0.80
0.06, 0.08, 0.10, 0.20, 0.30, 0.50

Table 5: Toxicity configurations in the DA-CRM simulation

In implementing the DA-CRM, dose set $\mathcal{D}$ contained six doses with monotonously increasing toxicity probabilities. A total of four toxicity scenarios were assumed and listed in Table 5. One skeleton was used for all scenarios where $(p_1, p_2, p_3, p_4, p_5, p_6) = (0.08, 0.12, 0.20, 0.30, 0.40, 0.50)$. Normal prior $\mathrm{N}(0, 2)$ was assumed for parameter α.

The DA-CRM procedure is the same with that of the EM-CRM stated in Section 2.2.1 with the sole difference being the calculation of toxicity probabilities in the 2nd step, where there's

no model selection/averaging problem (since a single skeleton is adopted through out the whole simulation). Thus we have,

$$\hat{\psi}_d = \int p_d^{\exp(\alpha)} g(\alpha|\mathbf{y}) \mathrm{d}\alpha, \quad d = 1, ..., D.$$

CHAPTER 3

A NEW METHOD – OD-CRM

With all the introduction on the importance and necessity of developing novel dose-finding methodologies in Section 1.2.3, in this chapter we shall illustrate the methodology OD-CRM (optimal design within the structure of CRM) in detail, along with associated theoretical results derived under various scenarios. [1]

3.1 OD-CRM in general MTD-identifying problems

We will study OD-CRM under general dose-finding setup (no delayed-response) for three models separately, namely, simple power model, two-parameter logistic model, and two-parameter probit model. In the following article we use upper-script and lower-script p, l, and pb to distinguish these models and their corresponding equations. As introduced in Chapter 1, we denote response Y to be a binary random variable where 1 indicates patient experiencing DLT and 0 otherwise. We also consider X to be the dose level assigned to each entered patient, where its realization x, determined by the resulting optimal designs, will take value from the dose level set $\mathcal{D} = \{d_1, ..., d_D\}$.

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[1] Part of this Chapter was published in two of the author's publications (52) and (53).

3.1.1 Simple power model

A simple power model is given by

$$Y \sim \text{Ber}(\psi^p(x, \alpha_p)), \quad \psi^p(x, \alpha_p) = \mathbf{E}(Y|X = x) = x^{\exp(\alpha_p)} \tag{3.1}$$

where

$$\alpha_p \in \mathsf{R} \text{ and } 0 < x < 1. \tag{3.2}$$

Note that here x in the model is the toxicity belief of its corresponding dose d that falls in between of 0 and 1, so that for any real α_p, we have $0 < p = x^{\exp(\alpha_p)} < 1$; and more importantly, $p|_{x_1} < p|_{x_2}$ when $x_1 < x_2$, thus the increasing monotonicity of dose level x and toxicity rate p is satisfied. The specific transformation of dose level d to its toxicity belief, called the "skeleton", was discussed in (9).

In a trail with the goal of identifying the MTD, we derive optimal dose allocations under simple power model through OD-CRM analytically. Corresponding result is presented in Theorem 1.

Theorem 1. *Under simple power model (Equation 3.1), for any parameter $\alpha_p \in \mathsf{R}$, regardless of the target toxicity rate p_t set in the trial, the optimal design always choose the dose level with the corresponding toxicity rate $\tilde{p}$, where $\tilde{p}$ is the solution to equation* $\log p + 2 - 2p = 0$.

Proof. Let $\beta_p = \exp(\alpha_p)$, then under design $\xi = \{(x_i, \omega_i), i = 1, ..., k\}$, the information matrix for β_p can be derived as follows,

$$\begin{aligned}\mathbf{I}^p(\beta_p) &= \sum_{i=1}^{k} \omega_i \, \mathbf{E}_{\beta_p} \left(-\frac{\partial^2 \log L_i(\beta_p|(x_i, y_i))}{\partial {\beta_p}^2} \right) \\ &= \sum_{i=1}^{k} w_i \, \frac{x_i^{\beta_p} (\log x_i)^2}{1 - x_i^{\beta_p}}\end{aligned}$$

where $L_i(\beta_p|(x_i, y_i))$ is the likelihood function of parameter β_p under each data point (x_i, y_i). We consider MTD as a function of β_p,

$$\mathrm{MTD}_p = b_p(\beta_p) = p_t^{1/\beta_p} \tag{3.3}$$

where p_t is the target toxicity rate. Then the asymptotic variance for $\widehat{\mathrm{MTD}} = b_p(\hat{\beta}_p)$ is

$$\mathbf{V} = \left[\left(p_t^{1/\beta_p} \right) (\ln p_t) \left(-\frac{1}{\beta_p^2} \right) \right]^2 \left[\sum_{i=1}^{k} \omega_i \, \frac{x_i^{\beta_p} (\log x_i)^2}{1 - x_i^{\beta_p}} \right]^{-1}.$$

As we discussed before, $\beta_p = \exp(\alpha_p)$ is substituted by its best guess under locally optimality context. Therefore, a design that puts all the weights on point x_0, where x_0 maximizes function

$$f(x) = \frac{x^{\beta_p} (\log x)^2}{1 - x^{\beta_p}},$$

is the optimal design that minimizes V; therefore we have $\xi_{opt} = \{(x_0, 1)\}$.

Substitute x in function f with p, where $x = p^{1/\beta_p}$ according to Equation 3.1, we have

$$f(x) = \frac{x^{\beta_p}(\log x)^2}{1 - x^{\beta_p}} = \left(\frac{1}{\beta_p}\right)^2 \frac{p\,(\log p)^2}{1-p}.$$

Note that maximizing function

$$g(p) = \frac{p\,(\log p)^2}{1-p}$$

on $p \in (0,1)$ is equivalent to maximizing function $f(x)$ on $x \in (0,1)$. Set

$$\frac{\mathrm{d}g(p)}{\mathrm{d}p} = \frac{\log p}{(1-p)^2}(\log p + 2 - 2p) = 0,$$

and let $\tilde{p}$ be the solution to the equation above. A numerical approximation to $\tilde{p}$ on $(0,1)$ is $\tilde{p} \approx 0.2032$. Since $(\log p)/(1-p)^2 < 0$ on $(0,1)$, $g(p)$ will be maximized at $\tilde{p}$ if we can show that $\log p + 2 - 2p$ is negative on $(0,\tilde{p})$ and positive on $(\tilde{p},1)$. We can easily check that $\log p + 2 - 2p$ is strictly increasing on $(0, 0.5)$ and strictly decreasing on $(0.5, 1)$. Consequently, $\log p + 2 - 2p$ must be negative on $(0,\tilde{p})$ and positive on $(\tilde{p}, 0.5)$. In addition, $\log p + 2 - 2p|_{p=1} = 0$ implies that $\log p + 2 - 2p > 0$ on $[0.5, 1)$. Thus point $\tilde{p}$ maximizes $g(p)$ on $(0,1)$. □

One may argue that it seems unreasonable to construct designs disregard of what the target p_t is. With that doubt in mind, the logic behind the result given in Theorem 1 is explained as follows. As mentioned in Section 1.1.2, when the dimension of model parameter is one, x in model ψ could be a dose label/dose transformation instead of the actual dose administered to patients, as long as the monotonicity between dose x and toxicity rate p is guaranteed.

Moreover, the one-parameter power model satisfies the requirement that there exists one and only one α_p such that $p = \psi(x, \alpha_p)$, which further promises the one-on-one map between α_p and $\text{MTD}|_{p_t}$ since MTD_{p_t} can be written as an one-on-one transformation of α_p given p_t, as shown in Equation 3.3. Therefore, an optimal design that givens the "best" estimation of model parameter α_p in the sense of asymptotic variance minimization, will at the same time provide us with the "most accurate" MTD estimate.

If the target toxicity rate in a medical trial is fixed at some other value, the corresponding efficiency loss is presented in Table 6. We can see from the result that as long as the target toxicity rate is chosen from a reasonable range, when compared to resulting designs constructed by the OD-CRM, the standard CRM procedure will generate a nearly optimal design with negligible efficiency loss.

p_t	0.10	0.15	0.20	0.25	0.30	0.35
Relative efficiency	0.910	0.981	0.999	0.990	0.960	0.916

Table 6: Relative efficiency under different target toxicity rate

However, the optimal design derived here is based on the asymptotic distribution of the MTD; whereas in practical circumstances, sample size is usually limited. Simulations targeted at a finite sample size are thus given here with the expectation to confirm designs built by

OD-CRM will perform well not only under an asymptotic structure, but in real life situations as well.

The simulations were conducted under power model (Equation 3.1) , $\alpha \in \mathsf{R}$, with $\beta = \exp(\alpha)$ being set to be 0.5 and 2, respectively. For each model, the performance of the standard CRM and that of the OD-CRM were compared under four different target toxicity rates: 0.15, 0.25, 0.3, and 0.35, all of which are practically common in Phase I clinical trials.

Target rate	Toxicity scenario					
$p_t = 0.15$	0.05	0.10	0.15	0.25	0.30	0.40
$p_t = 0.25$	0.05	0.10	0.20	0.30	0.40	0.50
$p_t = 0.3$	0.05	0.10	0.20	0.30	0.40	0.50
$p_t = 0.35$	0.15	0.2	0.3	0.37	0.40	0.50

Table 7: Toxicity configurations for testing on each different p_t

Notice that in a actual clinical studies, we may not have a dose level which exactly corresponds to the target toxicity rate. Bearing that in mind, cases where $p_t = 0.25$ and 0.35 in the simulation performed were targeted at the situation when p_t was not included in the true dose-toxicity correspondence from which data were generated. Table 7 lists the true toxicity rate setups for testing on each different p_t. For each value of p_t, we have six true toxicity rates and their corresponding dose levels (not shown in the table) from which data were simulated.

Under the case when $p_t = 0.25$, both dose levels 0.2 and 0.3 were considered to be the accurate MTD estimate; while for the case when $p_t = 0.35$, the accurate MTD estimate was considered to be the dose level corresponds to toxicity rate 0.37. Sample size was set at 24 with cohort size 3, and each scenario was repeated 1000 times. Results from the simulation are shown in Table 8. The entries in Table 8 consist of two values, where the first one represents the percentage of accurately identifying the MTD, and the second the percentage of toxicity occurrence.

Panel 1: $\beta = 0.5$

p_0	0.15	0.25	0.3	0.35
standard CRM	(0.505,0.217)	(0.762,0.304)	(0.422,0.348)	(0.335,0.386)
OD-CRM	(0.504,0.263)	(0.752,0.259)	(0.388,0.262)	(0.302,0.267)

Panel 2: $\beta = 2$

p_0	0.15	0.25	0.3	0.35
standard CRM	(0.567,0.134)	(0.803,0.213)	(0.464,0.260)	(0.358,0.307)
OD-CRM	(0.593,0.180)	(0.810,0.176)	(0.408,0.174)	(0.343,0.199)

Table 8: Comparison of performance of standard CRM and OD-CRM

The comparison results confirmed our counter-intuitive conclusion under the non-asymptotic structure. Under both models, performance of the standard CRM and the OD-CRM in terms of selecting the right dose level were comparable with small differences. Furthermore, under all scenarios except the one with $p_t = 0.15$, the percentage of toxicity occurrence of the OD-

CRM dropped by about 20%. This superiority is very intuitively understandable. Since the OD-CRM always operates on the point with the corresponding toxicity rate of 0.2, naturally it would generate less toxicity cases than the standard CRM procedure, where patients are assigned to dose levels with the corresponding toxicity rates greater than 0.2. However, when the target toxicity rate is set to be less than 0.2, the OD-CRM would be likely to have a higher percentage of toxicity occurrence than that of the standard CRM.

3.1.2 Two-parameter logistic model

A two-parameter logistic model is given by

$$Y \sim \text{Ber}(\psi^l(x, \theta_l)), \quad \psi^l(x, \theta_l) = \mathbf{E}(Y|X = x) = \frac{\exp(c_l)}{1 + \exp(c_l)}, \tag{3.4}$$

where $c_l = \alpha_l + \beta_l x$, $x > 0$, and

$$\beta_l > 0,\ \alpha_l < \log \frac{p_t}{1 - p_t} := c_{lt}. \tag{3.5}$$

The assumptions on the parameter are justified as follows. As in the simple power model case, we assume that the probability of toxicity p increases with increasing dose level x. From Equation 3.4, we can see that p is an increasing function with respect to c_l, thus to guarantee the increasing monotonicity of p and x, we should have $\beta_l > 0$. Moreover, it is expected that the target toxicity rate, p_t, cannot be lower than the toxicity rate at placebo level, i.e., $p|_{x=0}$. That is,

$$p_t > p|_{x=0} = \frac{\exp(\alpha_l)}{1 + \exp(\alpha_l)}.$$

Thus we shall have an upper bound for parameter α_l as in $\alpha_l < \log \frac{p_t}{1-p_t} = c_{lt}$. Note that α_l can be interpreted as the placebo effect while $c_{lt} = \log \frac{p_t}{1-p_t} = \alpha_l + \beta_l x_t$, is the MTD effect.

Now under design $\xi = \{(x_i, \omega_i), i = 1, ..., k\}$, the information matrix for $\theta_l = (\alpha_l, \beta_l)^T$ can be expressed as follows,

$$\mathbf{I}^l(\theta_l) = \sum_{i=1}^{k} \omega_i \, h_l(x_i, \theta_l) \, h_l^T(x_i, \theta_l)$$

where

$$h_l(x, \theta_l) = \left(\frac{\exp\left(\frac{c_l}{2}\right)}{1 + \exp(c_l)}, \frac{x \exp\left(\frac{c_l}{2}\right)}{1 + \exp(c_l)} \right)^T \stackrel{def}{=} \left(h_{l,1}(x, \theta_l), h_{l,2}(x, \theta_l) \right)^T. \tag{3.6}$$

Again, we write MTD as a function of θ_l, i.e.,

$$\text{MTD} \stackrel{def}{=} \eta_l = b_l(\theta_l) = \frac{1}{\beta_l} (c_{lt} - \alpha_l) \tag{3.7}$$

where we can see that the MTD is a scalar function of θ_l. Thus the c-optimality, which is designed to optimize the estimation of scalar combination of model parameter, is an appropriate choice here. The geometric approach provided by Elfving (17) is a powerful tool for identifying c-optimal designs. We present a version of the Elfving c-optimality theorem that suits our ongoing scenarios.

Elfving's theorem *Let Y be a random variable with expectation $E(Y)$, where a two-parameter model is used to depict the relationship between $E(Y)$ and x: $E(Y) = \varphi(x, \alpha, \beta)$; and the information matrix for $\theta = (\alpha, \beta)^T$ under design $\xi = \{(x_i, \omega_i), i = 1, ..., k\}$ can be expressed in the form of $I(\theta) = \sum_{i=1}^{k} w_i h(x_i, \theta) h^T(x_i, \theta)$, where h is a vector of dimension two.*

Let E denote the convex set of $\{h(x)\} \cup \{-h(x)\}$, $x \in \mathcal{X}$. Suppose we are interested in a scalar parameter $\eta = K^T\theta$ where K is a two-dimensional real constant vector, then the optimal design contains two points $h(x_1), h(x_2)$ (not necessarily different), such that the convex combination of them reach the boundary of the Elfving set E along the same direction of vector $K = \frac{\partial \eta}{\partial \theta}$.

Utilizing Elfving's method, we have the following theorem.

Theorem 2. *Under logistic model (Equation 3.4) with parameter assumptions (Equation 3.5), for any $0 < p_t < 0.5$, the optimal design for estimating the MTD is to collect data at the point of the MTD value estimated directly from the fitted dose-response curve.*

Proof. By directly applying Elfving's theorem given above, we know that the optimal design points $h_l(x_1), h_l(x_2)$, where function h_l is defined in Equation 3.6, are chosen such that the convex combination of them reach the boundary of the Elfving set $E^l = Conv\big\{\{h_l(x)\} \cup \{-h_l(x)\}\big\}$, $x > 0$, along the same direction of vector:

$$\frac{\partial \eta_l}{\partial \theta_l} = \frac{\partial b_l(\theta_l)}{\partial \theta_l} = \left(-\frac{1}{\beta_l}, -\frac{c_{lt} - \alpha_l}{\beta_l^2}\right)^T \stackrel{def}{=} (b_{l,1}^{'}, b_{l,2}^{'})^T. \tag{3.8}$$

An example of Elfving set under two-parameter logistic model is shown in Figure 1.

Since β_l is always positive, $b_{l,1}^{'}$ is thus negative. So vector $(b_{l,1}^{'}, b_{l,2}^{'})^T$ intersects with the Elfving set E^l only in the third quadrant. Now our goal is to find this intersection point of vector $(b_{l,1}^{'}, b_{l,2}^{'})^T$ and Elfving set E^l. We achieve this goal by proving the following lemma.

Lemma 1. *Under logistic model (Equation 3.4) with parameter assumptions (Equation 3.5), for any $0 < p_t < 0.5$, vector $(b_{l,1}^{'}, b_{l,2}^{'})^T$ defined in Equation 3.8 always intersects with the*

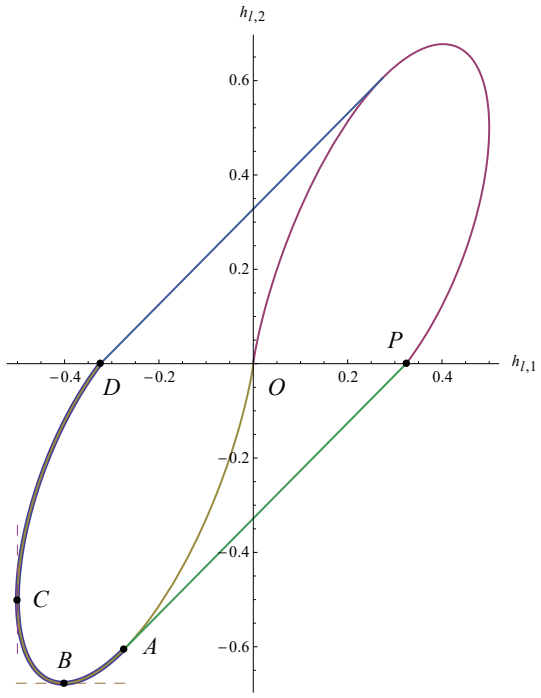


Figure 1: An Elfving set example under two-parameter logistic model

Elfving set E^l *on the part of the original lower curve* $\{-h_l(x)\}$ *(i.e., the bold part AD shown in Figure 1).*

Let

$$S_l(x) \overset{def}{=} \frac{h_{l,2}(x)}{h_{l,1}(x)} = \frac{x \exp\left(\frac{c_l}{2}\right)}{1+\exp(c_l)} \Bigg/ \frac{\exp\left(\frac{c_l}{2}\right)}{1+\exp(c_l)} = x \tag{3.9}$$

denote the slope of vector $(h_{l,1}(x), h_{l,2}(x))^T$ for $x \in \{\{h_l(x)\} \cup \{-h_l(x)\}\}$. It is easy to see that the slope of vector $(h_{l,1}(x), h_{l,2}(x))^T$ at the original lower curve (the AD part) equals the

x value of that point. Then it is equivalent to show that the direction of vector $(b'_{l,1}, b'_{l,2})^T$ falls between 0 and S_{x_A}, that is,

$$0 < \frac{b'_{l,2}}{b'_{l,1}} = \frac{c_{lt} - \alpha_l}{\beta_l} < S_l(x_A) = x_A, \tag{3.10}$$

with point $(h_{l,1}(x_A), h_{l,2}(x_A))$ being the tangent point on curve $\big\{ -h_l(x), x > 0 \big\}$, where the corresponding tangent line AP is the common tangent line of the two curves $\big\{h_l(x), x > 0\big\}$ and $\big\{ -h_l(x), x > 0 \big\}$, i.e., the lower boundary of the convex hull E^l. Hereafter in this proof, we refer to point $(h_{l,1}(x_A), h_{l,2}(x_A))$ described above as the tangent point A (as shown in Figure 1).

Note that here we consider the value of 0.5 as the upper bound for p_t because it is medically reasonable in most of the clinical trials. Since $p_t = \dfrac{\exp(c_{lt})}{1 + \exp(c_{lt})} < 0.5$, we have $c_{lt} < 0$. Now from the range of p_t and parameter assumptions stated in Equation 3.5, we have

$$\alpha_l < c_{lt} < 0 \quad \Rightarrow \quad 0 < \frac{1}{\beta_l}(c_{lt} - \alpha_l) < -\frac{\alpha_l}{\beta_l}.$$

The first inequality in Equation 3.10 is thus clear. In order to prove the second inequality, we only need to show that $-\dfrac{\alpha_l}{\beta_l} < x_A$. Let

$$H_l(x) = \frac{\partial(-h_{l,2}(x))}{\partial x} \Bigg/ \frac{\partial(-h_{l,1}(x))}{\partial x} = x + \frac{1 + \exp(c_l)}{\frac{\beta_l}{2}(1 - \exp(c_l))}$$

denote the slope of curve $\big\{ -h_l(x), x > 0 \big\}$ at each x. Then it is easy to see that $-\dfrac{\alpha_l}{\beta_l} := x_C$ is the point with slope being $+\infty/-\infty$ (point C shown in Figure 1). Although it is quite clear

from the graph that point A is to the right of point C which suggests that $x_C < x_A$, we still give a concise mathematical explanation to reinstate the conclusion rigorously.

With $H_l(x)$ defined above, we have

$$\frac{\mathrm{d}H_l(x)}{\mathrm{d}x} = 1 + \frac{4\exp(c_l)}{(1-\exp(c_l))^2} > 0 \text{ for all } x > 0,$$

which suggests an increasing pattern of function $H_l(x)$ with respect to x with a critical point C at $x_C = -\frac{\alpha_l}{\beta_l}$. We summarize the behavior of function $H_l(x)$ on $x \in [0, +\infty)$ in Table 9.

	Point D	Point C	Point B	Point O
x	0	$-\frac{\alpha_l}{\beta_l}$	x_B	$+\infty$
$H_l(x)$	$\frac{2(1+\exp(\alpha_l))}{\beta_l(1-\exp(\alpha_l))} > 0$	$+\infty/-\infty$	0	$+\infty$

Table 9: Lower curve slope change under logistic model

Note that $H_l(0) = \frac{2(1+\exp(\alpha_l))}{\beta_l(1-\exp(\alpha_l))} > 0$ is due to parameter assumptions stated in Equation 3.5. Since A is the tangent point on curve $\big\{-h_l(x), x > 0\big\}$, $H_l(A)$ is same as the slope of the tangent line PA, which serves as the lower boundary of the convex hull E^l thus connects curve $\big\{h_l(x), x > 0\big\}$ from the first quadrant to curve $\big\{-h_l(x), x > 0\big\}$ in the third quadrant. Therefore the slope of line PA is positive, so does $H_l(x_A)$. Then from Table 9 we know that

point A is either on curve DC, or curve BO, with the previous possibility ruled out due to the convex nature of the set E^l. So point A is to the right of point B, thus to the right of point C.

So far lemma 1 has been proved completely; and moving directly from the conclusion given in lemma 1, we know that under logistic model (Equation 3.4) with parameter assumptions (Equation 3.5), for any $0 < p_t < 0.5$, an optimal design contains only one point x, i.e., the intersection point of vector $(b'_{l,1}, b'_{l,2})^T$ and curve AD, with weight 1, which can be derived easily according to Equation 3.9:

$$x = S_l(x) = \frac{h_{l,2}(x,\theta_l)}{h_{l,1}(x,\theta_l)} = \frac{b'_{l,2}}{b'_{l,1}} = \left(-\frac{\log\frac{p_t}{1-p_t} - \alpha_l}{\beta_l^2}\right) \Big/ \left(-\frac{1}{\beta_l}\right) = \frac{1}{\beta_l}\left(c_{lt} - \alpha_l\right).$$

Compared with Equation 3.7, we can see that the optimal point x here is the same as the direct estimation of MTD from the dose-toxicity curve, thus complete the proof of Theorem 2. □

3.1.3 Two-parameter probit model

A two-parameter probit model is given by

$$Y \sim \text{Ber}(\psi^{pb}(x,\theta_{pb})), \quad \psi^{pb}(x,\theta_{pb}) = \mathbf{E}(Y|X=x) = \Phi(c_{pb}), \tag{3.11}$$

where $c_{pb} = \alpha_{pb} + \beta_{pb}x$, $x > 0$, and

$$\beta_{pb} > 0,\ \alpha_{pb} < \Phi^{-1}(p_t) := c_{pbt}. \tag{3.12}$$

Here Φ is the standard normal cumulative density function (cdf) and justification of assumptions on the parameter (Equation 3.12) is similar to the one given under logistic model, thus will not be shown again.

Similarly, under design $\xi = \{(x_i, \omega_i), i = 1, ..., k\}$, the information matrix for $\theta_{pb} = (\alpha_{pb}, \beta_{pb})^T$ can be expressed as follows,

$$\mathbf{I}^{pb}(\theta_{pb}) = \sum_{i=1}^{k} \omega_i \, h_{pb}(x_i, \theta_{pb}) \, h_{pb}^T(x_i, \theta_{pb})$$

where

$$h_{pb}(x, \theta_{pb}) = \left(\frac{\phi(c_{pb})}{\sqrt{\Phi(c_{pb})(1 - \Phi(c_{pb}))}}, \frac{x\phi(c_{pb})}{\sqrt{\Phi(c_{pb})(1 - \Phi(c_{pb}))}} \right)^T$$

and ϕ is the standard normal probability density function (pdf).

Again, we write MTD as a function of θ_{pb}, i.e.,

$$\text{MTD} \stackrel{def}{=} \eta_{pb} = b_{pb}(\theta_{pb}) = \frac{1}{\beta_{pb}} \left(c_{pbt} - \alpha_{pb} \right),$$

and utilize Elfving's theorem introduced in Section 3.1.2 to find the optimal design for identifying the MTD. A preliminary result is given in Theorem 3.

Theorem 3. *Under probit model (Equation 3.11) with parameter assumptions (Equation 3.12), for any $0 < p_t < 0.5$, the optimal design for estimating MTD is to collect data at the point of the MTD value estimated directly from the fitted dose-response curve.*

Proof. Following the same logic as in the proof under the logistic model case, here we have an Elfving set $E^{pb} = Conv\big\{\{h_{pb}(x)\} \cup \{-h_{pb}(x)\}\big\}$, $x > 0$, with the target vector and its direction being

$$\frac{\partial \eta_{pb}}{\partial \theta_{pb}} = \frac{\partial b_{pb}(\theta_{pb})}{\partial \theta_{pb}} = \left(-\frac{1}{\beta_{pb}}, -\frac{c_{pbt} - \alpha_{pb}}{\beta_{pb}^2}\right)^T \stackrel{def}{=} (b'_{pb,1}, b'_{pb,2})^T$$

and $\dfrac{b'_{pb,2}}{b'_{pb,1}} = \dfrac{c_{pbt} - \alpha_{pb}}{\beta_{pb}}$, respectively. Moreover, the slope of vector $(h_{pb,1}(x), h_{pb,2}(x))^T$ for $x \in \big\{\{h_{pb}(x)\} \cup \{-h_{pb}(x)\}\big\}$ can be calculated as

$$S_{pb}(x) \stackrel{def}{=} \frac{h_{pb,2}(x)}{h_{pb,1}(x)} = \frac{x\phi(c_{pb})}{\sqrt{\Phi(c_{pb})(1-\Phi(c_{pb}))}} \Bigg/ \frac{\phi(c_{pb})}{\sqrt{\Phi(c_{pb})(1-\Phi(c_{pb}))}} = x.$$

An example of an Elfving set under two-parameter probit model is shown in Figure 2.

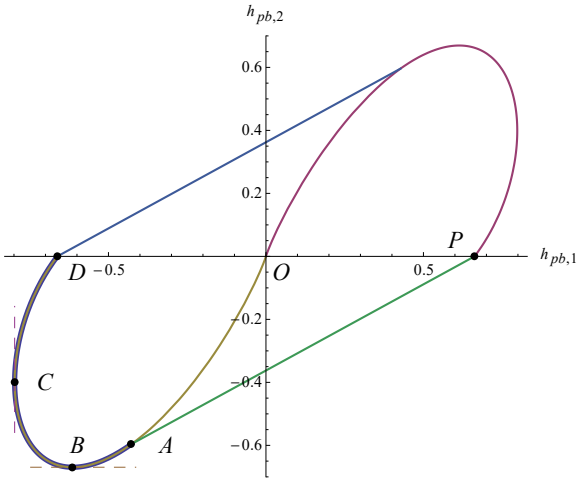


Figure 2: An Elfving set example under two-parameter probit model

By comparing the analysis components of the probit model with those of the logistic model, we say that these two models are very similarly structured in the sense that (i) their MTD expressions, $b(\theta)$ function, the target vector $\frac{\partial \eta}{\partial \theta}$ and its direction $\frac{b_2'}{b_1'}$, all share the same formula respectively, with corresponding MTD effect c_t; and (ii) their $h(x,\theta)$ vectors follow the same pattern as in $h_2(x) = x\, h_1(x)$, which makes them both have the property that the slope of vector $(h_1(x), h_2(x))^T$ at the original curve equals the x value of that point, i.e., $S(x) = x$. Therefore, the counterpart of lemma 1 for the probit model can be proved following similar arguments as in the logistic model case, with differences presented as follows.

We denote the slope of curve $\big\{ -h_{pb}(x), x > 0 \big\}$ at each x as

$$H_{pb}(x) = \frac{\partial(-h_{pb,2}(x))}{\partial x} \Bigg/ \frac{\partial(-h_{pb,1}(x))}{\partial x} = x + \frac{2}{\beta_{pb}(\mu(c_{pb}) - \lambda(c_{pb}) - 2c_{pb})}$$

where $\mu(c) = \dfrac{\phi(c)}{1-\Phi(c)}$ and $\lambda(c) = \dfrac{\phi(c)}{\Phi(c)}$. Then again $-\dfrac{\alpha_{pb}}{\beta_{pb}} := x_C$ is the point with slope being $+\infty/-\infty$ (point C shown in Figure 2) because $c_{pb}|_{x=x_C} = 0$ and $\mu(0) = \lambda(0) = \sqrt{\dfrac{2}{\pi}}$. Now we examine the behavior of $H_{pb}(x)$ on $[0, +\infty)$.

From conclusions given by Sampford (see (44) and (45)), $\mu(c) = \dfrac{\phi(c)}{1-\Phi(c)}$ is increasing and convex with oblique asymptote $y = c$; while $\lambda(c) = \dfrac{\phi(c)}{\Phi(c)}$ is decreasing and convex with oblique asymptote $y = -c$. Therefore, $\mu'(c)$ is positive and increasing while $\lambda'(c)$ is negative and increasing, both with respect to c. Then we have, $0 < \mu'(c) < 1$ and $0 < -\lambda'(c) < 1$. Thus

$$\frac{\mathrm{d}(\mu(c) - \lambda(c) - 2c)}{\mathrm{d}c} = \mu'(c) - \lambda'(c) - 2 < 1 + 1 - 2 < 0 \tag{3.13}$$

and

$$\frac{\mathrm{d}H_{pb}(x)}{\mathrm{d}x} = 1 - \frac{2}{(\mu(c) - \lambda(c) - 2c)^2}(\mu'(c) - \lambda'(c) - 2) > 0 \text{ for all } x > 0,$$

which again, suggests an increasing pattern of function $H_{pb}(x)$ with respect to x with a critical point C at $x_C = -\frac{\alpha_{pb}}{\beta_{pb}}$. We again summarize the behavior of function $H_{pb}(x)$ on $x \in [0, +\infty)$ in Table 10.

	Point D	Point C	Point B	Point O
x	0	$-\frac{\alpha_{pb}}{\beta_{pb}}$	x_B	$+\infty$
$H_{pb}(x)$	$\frac{2}{(\mu(\alpha_{pb}) - \lambda(\alpha_{pb}) - 2\alpha_{pb})\,\beta_{pb}} > 0$	$+\infty/-\infty$	0	$+\infty$

Table 10: Lower curve slope change under probit model

Note that $H_{pb}(0) = \frac{2}{(\mu(\alpha_{pb}) - \lambda(\alpha_{pb}) - 2\alpha_{pb})\,\beta_{pb}} > 0$ is due to the assumptions postulated on the model parameter stated in Equation 3.12, and the fact that $\mu(\alpha_{pb}) - \lambda(\alpha_{pb}) - 2\alpha_{pb} > \mu(0) - \lambda(0) - 2 \cdot 0 = 0$. With the same arguments as stated in the logistic model case, we know that the tangent point A is to the right of point C, which proves lemma 1 under probit model and further completes the prove of Theorem 3. □

As we can see from Theorem 2 and 3, our resulting designs coincide with the largely used dose selection method where the dose level assigned to the next allocated cohort is determined

by the MTD estimated from the newly fitted dose-toxicity curve. Therefore, we can see that under regular dose-finding setup, while the way of dose allocation in a standard CRM-based design is intuitively plausible, it turns out to be statistically the "best" from the optimal design point of view as well.

3.2 OD-CRM in MTD-identifying problems with late-onset toxicities

Following the description of dose-finding design setup with delayed responses present given in Section 1.3.2, here in this Section we study OD-CRM for the same three models. First, at each interim study time point t, we divide all enrolled patients into K groups, $\mathcal{X}_1, ..., \mathcal{X}_K$, with each group including all the patients who have been enrolled for k periods, $k = 1, ..., K$. After patients have been enrolled for an entire evaluation period $T = u_K$, we stop adding their enrollment time. Note that "enrollment time" here is counted at an individual level such that a patient may has been enrolled for k periods while the trial has been going on for a longer time.

For patient j who belongs to $\mathcal{X}_k$, we define a k-dim vector $Z_{j,k} = (Y_{j,1}, ..., Y_{j,k})$ to depict his/her behavior by time t. Then $Z_{j,k}$ follows a multinomial distribution that takes values from

$$\mathbf{1}^{(1)} := (1, 1, ..., 1), \mathbf{1}^{(2)} := (0, 1, ..., 1), ..., \mathbf{1}^{(k)} := (0, 0, ..., 0, 1) \text{ and } \mathbf{0}^{(k)} =: (0, ..., 0) \qquad (3.14)$$

where $\mathbf{1}^l$ denotes the event of first showing toxicity after enrollment time u_l, $l = 1, ..., k$; and $\mathbf{0}^k$ the event of showing no toxicity after being enrolled for k periods. Then we have, for $l = 1, ..., k$,

$$\begin{aligned}\mathsf{P}(Z_{j,k} = \mathbf{1}^l) &= \mathsf{P}(Y_{j,1} = \cdots = Y_{j,l-1} = 0, Y_{j,l} = \cdots = Y_{j,k} = 1) \\ &= \mathsf{P}(Y_{j,l-1} = 0, Y_{j,l} = 1) \\ &= (w_l - w_{l-1})\psi(x_j, \theta) = p_{x_j,l}.\end{aligned}$$

Note that the second equality stems from the fact that

$$\{Y_{j,l-1} = 0\} \subseteq \cdots \subseteq \{Y_{j,1} = 0\} \text{ and } \{Y_{j,l} = 1\} \subseteq \cdots \subseteq \{Y_{j,k} = 1\}.$$

Also,

$$\begin{aligned}\mathsf{P}(Z_{j,k} = \mathbf{0}^k) &= \mathsf{P}(Y_{j,1} = \cdots = Y_{j,k} = 0) \\ &= \mathsf{P}(Y_{j,k} = 0) \\ &= 1 - w_k\psi(x_j, \theta) = q_{x_j,k}.\end{aligned}$$

Note that $\sum_{l=1}^{k} p_{\cdot,l} + q_{\cdot,k} = 1$ for each $k = 1, ..., K$.
Now the overall likelihood and log-likelihood function by time t can be expressed as follows,

$$\begin{aligned}L(\theta) &= \prod_{k=1}^{K} \prod_{x \in \mathcal{X}_k} \left(\prod_{l=1}^{k} p_{x,l}^{\mathbf{1}_{\{Y_{x,k} = \mathbf{1}^l\}}} \cdot q_{x,k}^{\mathbf{1}_{\{Y_{x,k} = \mathbf{0}^k\}}} \right), \\ l(\theta) &= \sum_{k=1}^{K} \sum_{x \in \mathcal{X}_k} \left(\sum_{l=1}^{k} \mathbf{1}_{\{Y_{x,k} = \mathbf{1}^l\}} \log(p_{x,l}) + \mathbf{1}_{\{Y_{x,k} = \mathbf{0}^k\}} \log(q_{x,k}) \right).\end{aligned} \tag{3.15}$$

For the sake of calculating the MLE of θ, we summarize patients' contribution to the log-likelihood in Table 11, where for each $k = 1, ..., K$, $\mathcal{X}_k^l$ includes patients in the k^{th} group with observed response $Y_{\cdot,k} = \mathbf{1}^l$, $l = 1, ..., k$; while $\mathcal{X}_k^0$ includes patients in the k^{th} group with observed response $Y_{\cdot,k} = \mathbf{0}^k$.

Patient groups	Contribution to the log-likelihood
$\mathcal{X}_k^1$	$\log(p_{x,1})$
$\mathcal{X}_k^2$	$\log(p_{x,2})$
$\vdots$	$\vdots$
$\mathcal{X}_k^k$	$\log(p_{x,k})$
$\mathcal{X}_k^0$	$\log(q_{x,k})$

Table 11: Log-likelihood table

Notice that if two patients belong to $\mathcal{X}_{k_1}^{l_1}$ and $\mathcal{X}_{k_2}^{l_2}$, respectively; and $k_1 \neq k_2$, $0 < l_1 = l_2 = l \leq k_1, k_2$, then their contribution to the log-likelihood are in the same format as $\log(p_{x,l})$, where x represents their own dose level.

For the purpose of calculation, some equations/formulas are presented here for each $k = 1, ..., K$, $l = 1, ..., k$.

$$\mathbf{E}\left(\mathbf{1}_{\{Y_{x,k}=\mathbf{1}^l\}}\right) = p_{x,l} = (w_l - w_{l-1})\psi$$

$$\mathbf{E}\left(\mathbf{1}_{\{Y_{x,k}=\mathbf{0}^k\}}\right) = q_{x,k} = 1 - w_k\psi$$

$$\frac{\partial \log(p_{x,l})}{\partial \theta^T} = \begin{pmatrix} \frac{\partial \log((w_l - w_{l-1})\psi)}{\partial \alpha} & \frac{\partial \log((w_l - w_{l-1})\psi)}{\partial \beta} & \cdots \end{pmatrix} = \begin{pmatrix} \frac{\psi'_\alpha}{\psi} & \frac{\psi'_\beta}{\psi} & \cdots \end{pmatrix}$$

$$\frac{\partial \log(q_{x,k})}{\partial \theta^T} = \begin{pmatrix} \frac{\partial \log(1 - w_k\psi)}{\partial \alpha} & \frac{\partial \log(1 - w_k\psi)}{\partial \beta} & \cdots \end{pmatrix} = -\begin{pmatrix} \frac{w_k\psi'_\alpha}{1 - w_k\psi} & \frac{w_k\psi'_\beta}{1 - w_k\psi} & \cdots \end{pmatrix}$$

$$\frac{\partial^2 \log(p_{x,l})}{\partial\theta\partial\theta^T} = \begin{pmatrix} \frac{\partial^2 \log((w_l - w_{l-1})\psi)}{\partial^2\alpha} & \frac{\partial^2 \log((w_l - w_{l-1})\psi)}{\partial\alpha\partial\beta} & \cdots \\ \frac{\partial^2 \log((w_l - w_{l-1})\psi)}{\partial\alpha\partial\beta} & \frac{\partial^2 \log((w_l - w_{l-1})\psi)}{\partial^2\beta} & \cdots \\ \vdots & \vdots & \ddots \end{pmatrix}$$

$$= -\frac{1}{\psi^2} \begin{pmatrix} (\psi'_\alpha)^2 - \psi''_\alpha\psi & \psi'_\alpha\psi'_\beta - \psi''_{\alpha\beta}\psi & \cdots \\ \psi'_\alpha\psi'_\beta - \psi''_{\alpha\beta}\psi & (\psi'_\beta)^2 - \psi''_\beta\psi & \cdots \\ \vdots & \vdots & \ddots \end{pmatrix}$$

$$\frac{\partial^2 \log(q_{x,k})}{\partial\theta\partial\theta^T} = \begin{pmatrix} \frac{\partial^2 \log(1 - w_k\psi)}{\partial^2\alpha} & \frac{\partial^2 \log(1 - w_k\psi)}{\partial\alpha\partial\beta} & \cdots \\ \frac{\partial^2 \log(1 - w_k\psi)}{\partial\alpha\partial\beta} & \frac{\partial^2 \log(1 - w_k\psi)}{\partial^2\beta} & \cdots \\ \vdots & \vdots & \ddots \end{pmatrix}$$

$$= -\frac{1}{(1 - w_k\psi)^2} \begin{pmatrix} w_k\psi''_\alpha(1 - w_k\psi) + (w_k\psi'_\alpha)^2 & w_k\psi''_{\alpha\beta}(1 - w_k\psi) + w_k^2\psi'_\alpha\psi'_\beta & \cdots \\ w_k\psi''_{\alpha\beta}(1 - w_k\psi) + w_k^2\psi'_\alpha\psi'_\beta & w_k\psi''_\beta(1 - w_k\psi) + (w_k\psi'_\beta)^2 & \cdots \\ \vdots & \vdots & \ddots \end{pmatrix}$$

where as defined before, $\psi = \psi(x, \theta)$ is the toxicity probability and $\theta = (\alpha, \beta, \cdots)$ is the unknown model parameter.

Then the Fisher information matrix can be derived as follows,

$$
\begin{aligned}
\mathbf{I}(\theta) &= -\mathbf{E}\left(\frac{\partial^2 l(\theta)}{\partial\theta\partial\theta^T}\right) \\
&= \sum_{k=1}^{K}\sum_{x\in\mathcal{X}_k}\left(\sum_{l=1}^{k}\mathbf{E}\left(\mathbf{1}_{\{Y_{x,k}=\mathbf{1}^l\}}\right)\left(-\frac{\partial^2\log(p_{x,l})}{\partial\theta\theta^T}\right)+\mathbf{E}\left(\mathbf{1}_{\{Y_{x,k}=\mathbf{0}^k\}}\right)\left(-\frac{\partial^2\log(q_{x,k})}{\partial\theta\theta^T}\right)\right) \\
&= \sum_{k=1}^{K}\sum_{x\in\mathcal{X}_k}\sum_{l=1}^{k}\frac{w_l-w_{l-1}}{\psi}\begin{pmatrix} (\psi'_\alpha)^2-\psi''_\alpha\psi & \psi'_\alpha\psi'_\beta-\psi''_{\alpha\beta}\psi & \cdots \\ \psi'_\alpha\psi'_\beta-\psi''_{\alpha\beta}\psi & (\psi'_\beta)^2-\psi''_\beta\psi & \cdots \\ \vdots & \vdots & \ddots \end{pmatrix} \\
&\quad + \frac{1}{1-w_k\psi}\begin{pmatrix} w_k\psi''_\alpha(1-w_k\psi)+(w_k\psi'_\alpha)^2 & w_k\psi''_{\alpha\beta}(1-w_k\psi)+w_k^2\psi'_\alpha\psi'_\beta & \cdots \\ w_k\psi''_{\alpha\beta}(1-w_k\psi)+w_k^2\psi'_\alpha\psi'_\beta & w_k\psi''_\beta(1-w_k\psi)+(w_k\psi'_\beta)^2 & \cdots \\ \vdots & \vdots & \ddots \end{pmatrix} \\
&= \sum_{k=1}^{K}\sum_{x\in\mathcal{X}_k}\frac{w_k}{\psi(1-w_k\psi)}\begin{pmatrix} (\psi'_\alpha)^2 & (\psi'_\alpha)(\psi'_\beta) & \cdots \\ (\psi'_\alpha)(\psi'_\beta) & (\psi'_\beta)^2 & \cdots \\ \vdots & \vdots & \ddots \end{pmatrix}. \qquad (3.16)
\end{aligned}
$$

At any time point t, $\mathbf{I}(\theta)$ can be divided into two parts: (i) $\mathbf{I}_{\text{obs}}$, where $x \in \mathcal{X}_k$, $k = 2, ..., K$ are fixed/observed; and (ii) $\mathbf{I}_{\text{ran}}$, where $x \in \mathcal{X}_1$ determines the dose allocation for the newly-

enrolled patients, i.e., the design points of interest. In the following context, we use design $\xi = \{(x_d, \omega_d), d = 1, ..., D\}$ to denote dose allocation for each newly-enrolled cohort, where $x_1, ..., x_D$ are all the available doses each with corresponding weights ω_d, $d = 1, ..., D$, and $\sum_{d=1}^{D} \omega_d = 1$.

3.2.1 Simple power model

Under power model (Equation 3.1) with postulated assumptions on the parameter (Equation 3.2), we have

$$\psi'_\alpha(x, \alpha) = \frac{\partial x^{\exp(\alpha)}}{\partial \alpha} = x^{\exp(\alpha)} \log(x) \exp(\alpha).$$

Then under design $\{(x_d, \omega_d), d = 1, ..., D\}$, according to information matrix given in Equation 3.16, we have

$$\begin{aligned}\mathbf{I}^p(\alpha_p) &= \mathbf{I}^p_{\text{obs}}(\alpha_p) + \mathbf{I}^p_{\text{ran}}(\alpha_p) \\ &= \sum_{k=2}^{K} \sum_{x \in \mathcal{X}_k} \frac{w_k x^{\exp(\alpha_p)}}{1 - w_k x^{\exp(\alpha_p)}} (\log(x) \exp(\alpha_p))^2 + n \sum_{d=1}^{D} \omega_d \frac{w_1 x_d^{\exp(\alpha_p)}}{1 - w_1 x_d^{\exp(\alpha_p)}} (\log(x_d) \exp(\alpha_p))^2.\end{aligned} \tag{3.17}$$

where n is the size of each recruitment and w_1 is the first element in the weight function $w = (w_1, ..., w_K)$.

At any stage, $\mathbf{I}^p_{\text{obs}}(\alpha_p)$ is a fixed scaler; thus maximizing $\mathbf{I}^p(\alpha_p)$ in Equation 3.17 is equivalent to maximizing $\mathbf{I}^p_{\text{ran}}(\alpha_p)$ itself. Therefore, a design that puts all the weights on point x_d, where x_d maximizes function

$$f^p(x) = \frac{w_1 x^{\exp(\alpha)}}{1 - w_1 x^{\exp(\alpha)}} (\log(x) \exp(\alpha))^2,$$

is the optimal design that maximizes $\mathbf{I}^p_{\text{ran}}(\alpha)$. Thus, we have $\xi^p_{opt} = \{(x_d, 1)\}$.

Substitute x in function $f^p(x)$ with p, where $x = p^{1/\exp(\alpha)}$ according to power model (Equation 3.1), we have

$$f^p(p) = w_1 \cdot \frac{p(\log p)^2}{1 - w_1 p}.$$

Similar to the proof of Theorem 1, maximizing function

$$\tilde{f}^p(p) = \frac{p(\log p)^2}{1 - w_1 p}$$

on $p \in (0, 1)$ is mathematically equivalent to maximizing function $f^p(x)$ on $x \in (0, 1)$. Differentiate $\tilde{f}^p(p)$ with respect to p, we obtain

$$\frac{\mathrm{d}\tilde{f}^p(p)}{\mathrm{d}p} = \frac{\log p}{(1 - w_1 p)^2}(\log p + 2 - 2w_1 p) = 0.$$

Since $\dfrac{\log p}{(1 - w_1 p)^2} < 0$ for $p \in (0, 1)$, the solution p_d to equation

$$\log p + 2 - 2w_1 p = 0 \tag{3.18}$$

if exists, is the possible maximizer of $\tilde{f}^p(p)$; thus the corresponding $x_d = p_d^{\frac{1}{\exp(\alpha_p)}}$ is the targeting dose in ξ^p_{opt}. The following theorem shows that p_d exists, and is indeed the local maximizer of $\tilde{f}^p(p)$ on (0,1).

Theorem 4. *The solution to Equation 3.18, p_d, exists and maximizes $\tilde{f}^p(p)$ on (0,1).*

Proof. In order to prove that p_d exists, and is indeed the local maximizer of $\tilde{f}^p(p)$ on $(0,1)$, we need to show that $\frac{\mathrm{d}\tilde{f}^p(p)}{\mathrm{d}p}$ is positive on $(0,p_d)$ and negative on $(p_d,1)$. Remember that $\frac{\log p}{(1-w_1 p)^2} < 0$ for $p \in (0,1)$, thus we only need to show that $\log p + 2 - 2w_1 p$ is negative on $(0,p_d)$ and positive on $(p_d,1)$.

When $p \to 0$, $\log p + 2 - 2w_1 p \to -\infty$; when $p \to 1$, $\log p + 2 - 2w_1 p \to 2 - 2w_1 > 0$ since $w_1 \in (0,1)$. According to the intermediate value theorem, there exists at least one root for $\log p + 2 - 2w_1 p$ on $(0,1)$. Now we show that p_d is the only root for $\log p + 2 - 2w_1 p$ on $(0,1)$.

Taking derivative of $\log p + 2 - 2w_1 p$, we have

$$\frac{\mathrm{d}(\log p + 2 - 2w_1 p)}{\mathrm{d}p} = \frac{1}{p} - 2w_1 \overset{set}{=} 0 \Rightarrow p = \frac{1}{2w_1}.$$

Note that when $p \in (0, \frac{1}{2w_1})$, $\frac{1}{p} - 2w_1 > 0$; when $p \in (\frac{1}{2w_1}, \infty)$, $\frac{1}{p} - 2w_1 < 0$. Thus $\log p + 2 - 2w_1 p$ is strictly increasing on $(0, \frac{1}{2w_1})$, and strictly decreasing on $(\frac{1}{2w_1}, \infty)$. Moreover,

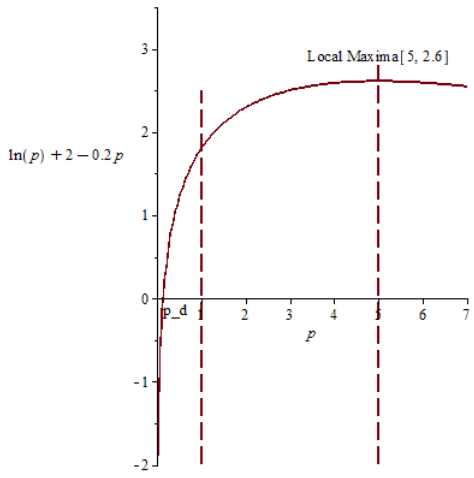
$$\log p + 2 - 2w_1 p|_{p=\frac{1}{2w_1}} = 1 - \log(2w_1) > 1 - \log 2 > 0.$$

Now on (0,1), $\log p + 2 - 2w_1 p$ behaves according to the following,

- If $\frac{1}{2w_1} \geq 1$, i.e., $w_1 \in (0, 0.5]$, $\log p + 2 - 2w_1 p$ starts from $-\infty$, passes through the p-axis at $p = p_d$ and continues to increase to point $(1, 2 - 2w_1)$.
- If $0 < \frac{1}{2w_1} < 1$, i.e., $w_1 \in (0.5, 1)$, $\log p + 2 - 2w_1 p$ starts from $-\infty$, passes through the p-axis at $p = p_d$, reaches its maximum at $p = \frac{1}{2w_1}$, and decreases to point $(1, 2 - 2w_1)$, which is still above the p-axis.

A comparison of these two cases is shown in Figure 3. Now under both circumstances, we have showed that $\log p + 2 - 2w_1 p$ is negative on $(0, p_d)$, and positive on $(p_d, 1)$. Thus complete the proof.

(a) When $w = 0.1$



(b) When $w = 0.6$

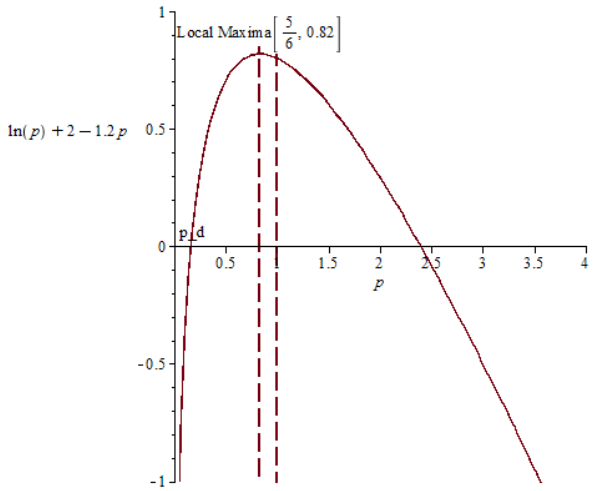


Figure 3: Behavior of $\log p + 2 - 2w_1 p$ under different w values

□

Result regarding the optimal dose allocation is given in the following theorem.

Theorem 5. *Under simple power model (Equation 3.1), for any parameter $\alpha^p \in \mathsf{R}$, the optimal design chooses the next dose level with the corresponding toxicity rate p^*, where p^* is the solution to equation* $\log p - 2w_1 p + 2 = 0$.

Notice that the optimal dose level depends on the estimate of the first-stage weight function w_1.

Binary general linear regression under two-parameter models

Before we move onto logistic and probit model, we first summarize some facts for binary general linear regression under two-parameter regression models.

At the first stage of a study trial, $\mathbf{I}_{\text{obs}}(\theta)$ is a zero matrix which makes $\mathbf{I}(\theta) = \mathbf{I}_{\text{ran}}(\theta)$. Then for a given design $\xi = \{(x_d, \omega_d), d = 1, ..., D\}$, $\sum_{d=1}^{D} \omega_d = 1$, let $c_d = \alpha + \beta x_d$, suppose the Fisher information matrix for parameter $\theta = (\alpha, \beta)$ can be written as

$$\mathbf{I}_{\xi}(\theta) = \sum_{d=1}^{D} \omega_d \cdot w_1 h(c_d, w_1) \begin{pmatrix} 1 & x_d \\ x_d & x_d^2 \end{pmatrix},$$

which can be rearranged as

$$\mathbf{I}_{\xi}(\theta) = A^T(\alpha, \beta) C_{\xi}(\alpha, \beta) A(\alpha.\beta) \tag{3.19}$$

where

$$A(\alpha, \beta) = \begin{pmatrix} w_1^{\frac{1}{2}} & -\frac{\alpha}{\beta} w_1^{\frac{1}{2}} \\ 0 & \frac{1}{\beta} w_1^{\frac{1}{2}} \end{pmatrix}$$

and

$$C_\xi(\alpha,\beta)=\sum_{d=1}^{D}\omega_d\left[\begin{pmatrix} g_1(c_d)\\ \\ g_2(c_d)\end{pmatrix}\begin{pmatrix} g_1(c_d) & g_2(c_d)\end{pmatrix}\right]=\begin{pmatrix} \sum_{d=1}^{D}\omega_d\Psi_1(c_d) & \sum_{d=1}^{D}\omega_d\Psi_2(c_d)\\ \sum_{d=1}^{D}\omega_d\Psi_2(c_d) & \sum_{d=1}^{D}\omega_d\Psi_3(c_d)\end{pmatrix} \tag{3.20}$$

in which (consider w_1 as fixed)

$$g_1(c_d)=h^{\frac{1}{2}}(c_d),\quad g_2(c_d)=c_dg_1(c_d)=c_dh^{\frac{1}{2}}(c_d),$$

and

$$\Psi_1(c_d)=g_1^2(c_d)=h(c_d),\quad \Psi_2(c_d)=c_dg_1^2(c_d)=c_dh(c_d),\quad \Psi_3(c_d)=c_d^2g_1^2(c_d)=c_d^2h(c_d).$$

Next, we'll discuss the optimal design construction under two-parameter logistic model and two-parameter probit model, respectively.

3.2.2 Two-parameter logistic model

Under logistic model (Equation 3.4), we have

$$h^l(c) = \frac{\exp(c)}{(1+\exp(c))^2(1+(1-w_1)\exp(c))},$$
$$g_1^l(c) = (h^l(c))^{\frac{1}{2}} = \frac{\exp(\frac{c}{2})}{(1+\exp(c))\sqrt{1+(1-w_1)\exp(c)}},$$
$$g_2^l(c) = c\,(h^l(c))^{\frac{1}{2}} = \frac{c\,\exp(\frac{c}{2})}{(1+\exp(c))\sqrt{1+(1-w_1)\exp(c)}},$$

and

$$\Psi_1^l(c) = h^l(c) = \frac{\exp(c)}{(1+\exp(c))^2(1+(1-w_1)\exp(c))},$$
$$\Psi_2^l(c) = ch^l(c) = \frac{c\exp(c)}{(1+\exp(c))^2(1+(1-w_1)\exp(c))},$$
$$\Psi_3^l(c) = c^2h^l(c) = \frac{c^2\exp(c)}{(1+\exp(c))^2(1+(1-w_1)\exp(c))}.$$

We construct optimal designs based on results derived by Yang and Stufken (57). First we show that $(\Psi_1^l(c), \Psi_2^l(c), \Psi_3^l(c))$ are Type I or Type II functions on $[A^l, B^l]$, where $[A^l, B^l]$ is the range for the transformed dose level c. Following is our choice for $[A^l, B^l]$ and the related justifications.

Under logistic model (Equation 3.4), the relationship between toxicity probability p and the transformed dose level c is

$$p = \frac{\exp(c)}{1+\exp(c)}$$

where p is increasing with respect to c.

For ethical reasons, the toxicity probability p can not be set too high. Here, we adopt $1/3$ as an upper bound for p, which will give an equivalent upper bound of $-\log 2$ for c. Then we decide on the lower bound. Notice that when $c \to -10$, $p \to 4.5E-5$, which is nearly 0. Thus we adopt -10 as lower bound for c. Consequently, the range for the transformed dose level c, $[A^l, B^l]$, can set to be any subset of $[-10, -\log 2]$, i.e., $[A^l, B^l] \subset [-10, -\log 2]$.

Taking first derivatives with respect to c, we want to examine the values of the expressions of $(\Psi_1^l(c))'$, $\left(\frac{(\Psi_2^l(c))'}{(\Psi_1^l(c))'}\right)'$, and $\left(\left(\frac{(\Psi_3^l(c))'}{(\Psi_1^l(c))'}\right)' \Big/ \left(\frac{\Psi_2^l(c)}{(\Psi_1^l(c))'}\right)'\right)'$, which are all too complicated to study analytically. Thus we use graphing tools to check whether or not they satisfy all the required conditions stated in (57). More specifically, we increase w_1 by 0.01 from 0 to 1 and graph each of these three functions against c, which ranges from -10 to $-\log 2$. By numerical checking, we have the following inference. For all $w_1 \in (0,1)$, $(\Psi_1^l(c))'$, $\left(\frac{(\Psi_2^l(c))'}{(\Psi_1^l(c))'}\right)'$, and $\left(\left(\frac{(\Psi_3^l(c))'}{(\Psi_1^l(c))'}\right)' \Big/ \left(\frac{\Psi_2^l(c)}{(\Psi_1^l(c))'}\right)'\right)'$ are all positive functions, which lead to a positive product for all $c \in [A^l, B^l] \subseteq [-10, -\log 2]$ (numeral checking graphs are partly shown in Figure 4), which further renders $(\Psi_1^l(c), \Psi_2^l(c), \Psi_3^l(c))$ as Type II functions on $[A^l, B^l] \subseteq [-10, -\log 2]$. Then following Lemma 3 given in Yang and Stufken (57), the optimal design under logistic model (Equation 3.4) is $\xi_{opt}^l = \{(c_d^l, \omega_d^l), (B^l, 1-\omega_d^l)\}$, where $c_d^l \in [A^l, B^l)$.

Now we derive analytical results under D-optimality. First, when there are only two optimal design points present, D-optimality will put equal weights for both design points, i.e., $\omega_d^l = 0.5$, and $\xi_{D-opt}^l = \{(c_d^l, 0.5), (B^l, 0.5)\}$. We now derive the choice of c_d^l.

The upper legend is the w_1 value and the lower one is the minimum value of the product function on $[-10, -\log 2]$.

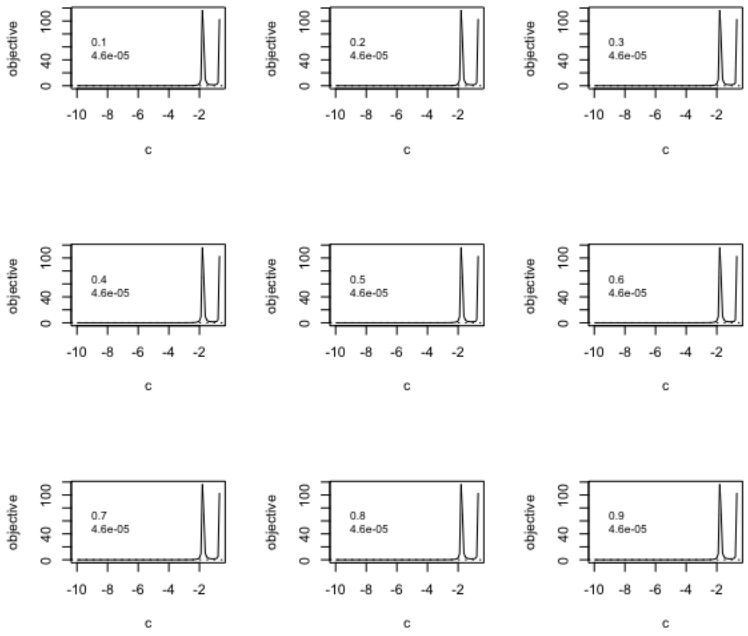


Figure 4: Behavior of the product for logistic model under nine w_1 values

Rewriting $C_{\xi^l_{D-opt}}(\alpha, \beta)$ in Equation 3.20 as

$$C_{\xi^l_{D-opt}}(\alpha, \beta) = \begin{pmatrix} g_1^l(c_d^l) & g_1^l(B^l) \\ g_2^l(c_d^l) & g_2^l(B^l) \end{pmatrix} \begin{pmatrix} 0.5 & 0 \\ 0 & 0.5 \end{pmatrix} \begin{pmatrix} g_1^l(c_d^l) & g_2^l(c_d^l) \\ g_1^l(B^l) & g_2^l(B^l) \end{pmatrix},$$

then ignoring terms independent of c_d^l, we re-express $|\mathbf{I}_{\xi_{D-opt}^l}(\theta_l)|$ in Equation 3.19 up-to-a-constant as

$$|\mathbf{I}_{\xi_{D-opt}^l}(\theta_l)| \propto \begin{vmatrix} g_1^l(c_d^l) & g_1^l(B^l) \\ g_2^l(c_d^l) & g_2^l(B^l) \end{vmatrix}^2 = (g_1^l(B^l))^2 \, (g_1^l(c_d^l)(B^l - c_d^l))^2.$$

Since $(g_1^l(B^l))^2 > 0$, it is easy to see that the targeting c_d^l in ξ_{D-opt}^l is the maximizer of the following function on $[A^l, B^l)$,

$$f^l(c) = (g_1^l(c)(B^l - c))^2 = \frac{\exp(c)(B^l - c)^2}{(1+\exp(c))^2(1+(1-w_1)\exp(c))}.$$

The following theorem provides the local maximizer of $f^l(c)$ on $[A^l, B^l)$.

Theorem 6. *Function $f^l(c)$ has exactly one maximum point, c_d^l, on any $[A^l, B^l) \subset [-10, -\log 2]$.*

Proof. Since $f^l(c) \geq 0$ with right boundary $f^l(B^l) = 0$, $f^l(c)$ is decreasing to the near left of point B^l. In order to show that it has exactly one maximum point on any $[A^l, B^l) \subset [-10, -\log 2]$, we only need to show that $f^l(c)$ is either (i) increasing on $[-10, c^*]$ and then decreasing on $[c^*, B^l)$; or (ii) decreasing on $[-10, B^l)$. Therefore, $\dfrac{\mathrm{d}f^l(c)}{\mathrm{d}c}$ has at most one root on $[-10, B^l)$.

Differentiating $f^l(c)$ with respect to c, we obtain

$$\frac{\mathrm{d}f^l(c)}{\mathrm{d}c} = \frac{\exp(c)(B^l - c)}{(1+(1-w_1)\exp(c))^2(1+\exp(c))^3} \cdot \tilde{f}^l(c),$$

where

$$\tilde{f}^l(c) = 2(1-w_1)(c-B^l-1)\exp(2c) + (c-B^l-2-2(1-w_1))\exp(c) + B^l - c - 2. \quad (3.21)$$

Since $\dfrac{\exp(c)(B^l-c)}{(1+(1-w_1)\exp(c))^2(1+\exp(c))^3} > 0$ for $c \in [A^l, B^l)$, we only need to show that $\tilde{f}^l(c)$ is monotone on $[-10, B^l)$.

Taking derivative of $\tilde{f}^l(c)$ with respect to c, we have

$$\frac{\mathrm{d}\tilde{f}^l(c)}{\mathrm{d}c} = 2(1-w_1)(2(c-B^l)-1)\exp(2c) + (c-B^l-2(1-w_1)-1)\exp(c) - 1 < 0$$

for all $w_1 \in (0,1)$ and $c \in [-10, B^l)$, which shows that $\tilde{f}^l(c)$ is strictly decreasing on $[-10, B^l)$; thus completes the proof. □

At $c = B^l$, we have $\tilde{f}^l(B^l) = -2(1-w_1)\exp(2B^l) - 2(2-w_1)\exp(B^l) - 2 < 0$, thus the behavior of $f^l(c)$ depends on the value of $\tilde{f}^l(A^l) = (1-\exp(A^l) - 2(1-w_1)\exp(2A^l))(B^l - A^l) - 2(1+\exp(A^l))(1+(1-w_1)\exp(A^l))$. With definition of functions

$$d_1(A^l) = \frac{2(1+\exp(A^l))(1+(1-w_1)\exp(A^l))}{(1-\exp(A^l)-2(1-w_1)\exp 2A)} \quad (3.22)$$

and

$$d_2(A^l) = \frac{(2-\log 2 - A^l)\exp(A^l) + 2 + \log 2 + A^l}{2e^{A^l}[(A^l+\log 2 - 1)\exp(A^l) - 1]}, \quad (3.23)$$

To summarize the behavior of $f^l(c)$ on any $[A^l, B^l) \subset [-10, -\log 2]$, the following two scenarios are presented here:

(I). when $1-d_2(A^l) \leq w_1$ and $B^l \geq A^l + d_1(A^l)$, $\tilde{f}^l(A^l) \geq 0$, $\tilde{f}^l(c)$ has one root, $c_d^l \in [A^l, B^l)$, which maximizes $f^{pb}(c)$ on $[A^l, B^l)$;

(II). when (i) $1 - d_2(A^l) \leq w_1$ and $B^l < A^l + d_1(A^l)$, or (ii) $1 - d_2(A^l) > w_1$, $\tilde{f}^l(A^l) < 0$, which makes $f^l(c)$ decreasing on $[A^l, B^l)$. Thus $c_d^l = A^l$ maximizes $f^l(c)$ on $[A^l, B^l)$.

Result regarding the optimal dose allocation is given in the following theorem.

Theorem 7. *At the first stage, under logistic model (Equation 3.4), for any transformed dose range $c = \alpha^l + \beta^l x \in [A^l, B^l] \subseteq [-10, -\log 2]$, the D-optimal dose assignment is*

$$\xi_{D-opt}^l = \{(c^*, 0.5), (B^l, 0.5)\},$$

and the choice of c^* would be one of the following two cases:

- *When $1 - d_2(A^l) < w_1$ and $B^l > A^l + d_1(A^l)$, $c^* \in (A^l, B^l)$ is the solution to equation $\tilde{f}^l(c) = 0$;*
- *Otherwise, $c^* = A^l$.*

Functions $\tilde{f}^l(c)$, $d_1(A)$, and $d_2(A)$ are defined in Equation 3.21, Equation 3.22, and Equation 3.23, respectively.

Notice that the optimal dose level still depends on the estimate of the first-stage weight function w_1.

3.2.3 Two-parameter probit model

Under probit model (Equation 3.11), we have

$$
\begin{aligned}
h^{pb}(c) &= \frac{\phi^2(c)}{\Phi(c)(1-w_1\Phi(c))},\\
g_1(c) &= (h^{pb}(c))^{\frac{1}{2}} = \frac{\phi(c)}{\sqrt{\Phi(c)(1-w_1\Phi(c))}},\\
g_2(c) &= c\,(h^{pb}(c))^{\frac{1}{2}} = \frac{c\phi(c)}{\sqrt{\Phi(c)(1-w_1\Phi(c))}},
\end{aligned}
$$

and

$$
\begin{aligned}
\Psi_1^{pb}(c) &= h^{pb}(c) = \frac{\phi^2(c)}{\Phi(c)(1-w_1\Phi(c))},\\
\Psi_2^{pb}(c) &= ch^{pb}(c) = \frac{c\phi^2(c)}{\Phi(c)(1-w_1\Phi(c))},\\
\Psi_3^{pb}(c) &= c^2h^{pb}(c) = \frac{(c\phi(c))^2}{\Phi(c)(1-w_1\Phi(c))}.
\end{aligned}
$$

Similar to the case of logistic model, by numerical checking, we have the following conclusion. For all $w_1 \in (0,1)$, $(\Psi_1^{pb}(c))'$, $\left(\frac{(\Psi_2^{pb}(c))'}{(\Psi_1^{pb}(c))'}\right)'$, and $\left(\left(\frac{(\Psi_3^{pb}(c))'}{(\Psi_1^{pb}(c))'}\right)' \Big/ \left(\frac{\Psi_2^{pb}(c)}{(\Psi_1^{pb}(c))'}\right)'\right)'$ are all positive functions, which lead to a positive product for all $c \in [A^{pb}, B^{pb}] \subseteq [-10, B_0^{pb}]$, where B_0^{pb} is the solution to function $-2c - \lambda(c) = 0$ and $\lambda(c) = \frac{\phi(c)}{\Phi(c)}$ is defined in Section 3.1.3 (numeral checking graphs are partly shown in Figure 5). Now that we have numerically showed that $(\Psi_1^{pb}(c), \Psi_2^{pb}(c), \Psi_3^{pb}(c))$ are Type II functions on $[A, B] \subseteq [-10, B_0^{pb}]$, then again,

following Lemma 3 given in Yang and Stufken (57), the optimal design under probit model (Equation 3.11) is $\xi_{opt}^{pb} = \{(c_d^{pb}, \omega_d^{pb}), (B^{pb}, 1 - \omega_d^{pb})\}$, where $c_d^{pb} \in [A^{pb}, B^{pb})$.

The upper legend is the w_1 value and the lower one is the minimum value of the product function on $[-10, B_0^{pb}]$.

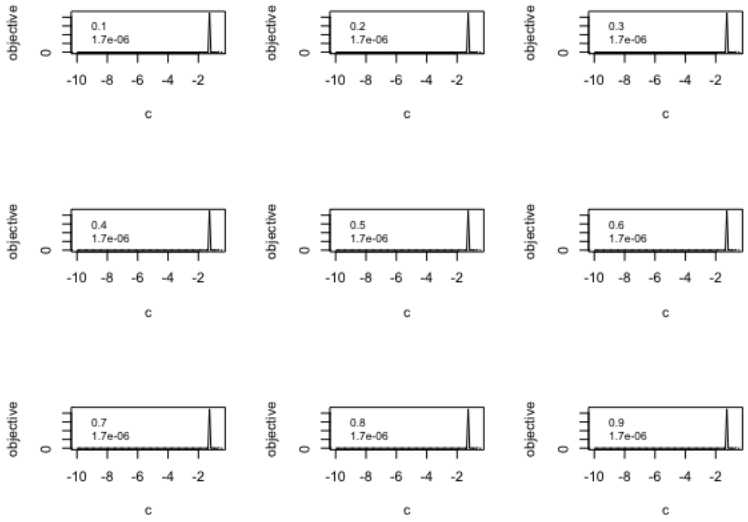


Figure 5: Behavior of the product for probit model under nine w_1 values

Analytical results under D-optimality will again render $\omega_d^{pb} = 0.5$, and $\xi_{D-opt}^{pb} = \{(c_d^{pb}, 0.5), (B^{pb}, 0.5)\}$. We now derive the choice of c_d^{pb}.

Following similar arguments stated in the logistic model case, we have

$$|\mathbf{I}_{\xi^{pb}_{D-opt}}(\theta_{pb})| \propto \begin{vmatrix} g_1^{pb}(c_d^{pb}) & g_1^{pb}(B^{pb}) \\ g_2^{pb}(c_d^{pb}) & g_2^{pb}(B^{pb}) \end{vmatrix}^2 = (g_1^{pb}(B^{pb}))^2 (g_1^{pb}(c_d^{pb})(c_d^{pb} - B^{pb}))^2,$$

and the targeting c_d^{pb} in ξ^{pb}_{D-opt} is the maximizer of the following function on $[A^{pb}, B^{pb})$,

$$f^{pb}(c) = (g_1^{pb}(c)(B^{pb} - c))^2 = \frac{((B^{pb} - c)\phi(c))^2}{\Phi(c)(1 - w_1\Phi(c))}.$$

The following theorem provides the local maximizer of $f^{pb}(c)$ on $[A^{pb}, B^{pb})$.

Theorem 8. *Function $f^{pb}(c)$ has exactly one maximum point, c_d^{pb}, on any $[A^{pb}, B^{pb}) \subset [-10, B_0^{pb})$.*

Proof. We rewrite $f^{pb}(c)$ as

$$f^{pb}(c) = \frac{(c - B^{pb})^2}{w_1}\,\lambda(c)\,\mu_w(c)$$

where

$$\lambda(c) = \frac{\phi(c)}{\Phi(c)}, \quad \mu_w(c) = \frac{w_1\phi(c)}{1 - w_1\Phi(c)}. \tag{3.24}$$

Notice that $\mu_{w_1=1}(c)$ is the same as function $\mu(c)$ defined in Section 3.1.3. Since $f^{pb}(c) \geq 0$ with right boundary $f^{pb}(B^{pb}) = 0$, $f^{pb}(c)$ is decreasing to the near left of point B^{pb}. In order to show that it has exactly one maximum point on any $[A^{pb}, B^{pb}) \subset [-10, B_0^{pb})$, we only need to show that $f^{pb}(c)$ is either (i) increasing on $[-10, c^*]$ and then decreasing on $[c^*, B_0^{pb})$; or (ii) decreasing on $[-10, B_0^{pb})$. That is to say, $\dfrac{\mathrm{d}f^{pb}(c)}{\mathrm{d}c}$ has at most one root on $[-10, B_0^{pb})$.

Using the fact that $\phi'(c) = -c\phi(c)$ and $\Phi'(c) = \phi(c)$, we have

$$\lambda'(c) := \frac{\mathrm{d}\lambda(c)}{\mathrm{d}c} = -\frac{c\phi(c)}{\Phi(c)} - \left(\frac{\phi(c)}{\Phi(c)}\right)^2 = -\lambda(c)(\lambda(c)+c),$$
$$\mu'_w(c) := \frac{\partial \mu_w(c)}{\partial c} = -\frac{cw_1\phi(c)}{1-w_1\Phi(c)} - \frac{w_1\phi(c)(-w_1\phi(c))}{(1-w_1\Phi(c))^2} = \mu_w(c)(\mu_w(c)-c).$$

Therefore,

$$\begin{aligned}\frac{\mathrm{d}f^{pb}(c)}{\mathrm{d}c} &= \frac{2(c-B^{pb})}{w_1}\,\lambda(c)\,\mu_w(c) + \frac{(c-B^{pb})^2}{w_1}\,\lambda'(c)\,\mu_w(c) + \frac{(c-B^{pb})^2}{w_1}\,\lambda(c)\,\mu'_w(c)\\ &= \frac{(c-B^{pb})}{w_1}\,\lambda(c)\,\mu_w(c)\,\left[2+(c-B^{pb})(\mu_w(c)-\lambda(c)-2c)\right].\end{aligned}$$

Now we need to prove that $2+(c-B^{pb})(\mu_w(c)-\lambda(c)-2c)$ has at most one root on $[-10, B_0^{pb})$. It suffices to show that

$$\tilde{f}^{pb}(c) = (c-B^{pb})(\mu_w(c)-\lambda(c)-2c) \tag{3.25}$$

is monotone on $[-10, B_0^{pb})$. Since

$$\frac{\partial \mu_w(c)}{\partial w_1} = \frac{\phi(c)}{1-w_1\Phi(c)}\left(1+\frac{w_1\Phi(c)}{1-w_1\Phi(c)}\right) > 0,$$

we have

$$\mu'_w(c) = \mu_w(c)(\mu_w(c)-c) < \mu_{w_1=1}(c)(\mu_{w_1=1}(c)-c) = \mu(c)(\mu(c)-c) = \mu'(c).$$

Thus we have $\mu_w'(c) - \lambda'(c) - 2 < \mu'(c) - \lambda'(c) - 2 < 0$, as already proved in Equation 3.13. Also,

$$\mu_w(c) - \lambda(c) - 2c > \mu_{w_1=0}(c) - \lambda(c) - 2c = -\lambda(c) - 2c > -\lambda(c) - 2c|_{c=B_0^{pb}} = 0.$$

Since $c < B^{pb}$, we have

$$\frac{\mathrm{d}\tilde{f}^{pb}(c)}{\mathrm{d}c} = (\mu_w(c) - \lambda(c) - 2c) + (c - B^{pb})(\mu_w'(c) - \lambda'(c) - 2) > 0,$$

which shows that $\tilde{f}^{pb}(c)$ is monotone (in fact increasing) on $[-10, B_0^{pb})$, thus completes the whole proof.

□

Now the actual behavior of $f^{pb}(c)$ depends on the values of A^{pb} and B^{pb}. Let

$$\min\{(c-B^{pb})(\mu_w(c)-\lambda(c)-2c)\} = (c-B^{pb})(\mu_w(c)-\lambda(c)-2c)|_{c=A^{pb}} = (A^{pb}-B^{pb})(\mu_w(A^{pb})-\lambda(A^{pb})-2A^{pb}),$$

we present the following two scenarios:

(I). When $(A^{pb} - B^{pb})(\mu_w(A^{pb}) - \lambda(A^{pb}) - 2A^{pb}) \leq -2$, $2 + (c - B^{pb})(\mu_w(c) - \lambda(c) - 2c) = 0$ has one root, $c_d^{pb} \in [A^{pb}, B^{pb})$, which maximizes $f^{pb}(c)$ on $[A^{pb}, B^{pb})$;

(II). When $(A^{pb} - B^{pb})(\mu_w(A^{pb}) - \lambda(A^{pb}) - 2A^{pb}) > -2$, $2 + (c - B^{pb})(\mu_w(c) - \lambda(c) - 2c) > 0$ on $[A^{pb}, B^{pb})$, which makes $f^{pb}(c)$ decreasing on $[A^{pb}, B^{pb})$. Thus $c_d^{pb} = A^{pb}$ maximizes $f^{pb}(c)$ on $[A^{pb}, B^{pb})$.

Result regarding the optimal dose allocation is given in the following theorem.

Theorem 9. *At the first stage, under probit model (Equation 3.11), for any transformed dose range* $c = \alpha + \beta x \in [A^{pb}, B^{pb}] \subseteq [-10, B_0^{pb}]$*, the D-optimal dose assignment is*

$$\xi_{D-opt}^{pb} = \{(c^*, 0.5), (B^{pb}, 0.5)\},$$

and the choice of c^* *would be one of the following two cases:*

- *When* $(A^{pb} - B^{pb})(\mu_w(A^{pb}) - \lambda(A^{pb}) - 2A^{pb}) < -2$, $c^* \in (A^{pb}, B^{pb})$ *is the solution to equation* $\tilde{f}^{pb}(c) + 2 = 0$*;*
- *Otherwise,* $c^* = A^{pb}$*.*

Functions $\mu_w(c)$, $\lambda(c)$, *and* $\tilde{f}^{pb}(c)$, *are defined in Equation 3.24, and Equation 3.25, respectively.*

Notice that the optimal dose level still depends on the estimate of the first-stage weight function w_1.

CHAPTER 4

SIMULATION STUDIES

All analytic results derived and presented in Chapter 3 are built under the constraints that either (a) the assuming working model is one-dimension so that information matrices are scalars which eliminates the affect of existing designs since optimizing $\mathbf{I}_{\text{new}} + \mathbf{I}_{\text{exist}}$ is equivalent to optimizing $\mathbf{I}_{\text{new}}$ itself; or (b) only first-stage designs are being constructed so that $\mathbf{I}_{\text{exist}} = 0$ and related D-optimality conclusions can be established with the help of matrix-determinant manipulation and optimality results for two-parameter models given in Yang and Stufken (57). Moreover, when more than one working models are to be brought into the process of design construction, giving theoretical results become infeasible due to the complication in the formulation of Fisher infromation matrices.

Therefore, in order to obtain optimal dose allocations for a broader design setup, meaning multi-stage, multiple working models, different parameter targets, and an unified Φ_p optimality criterion, we need a general and efficient algorithm that can quickly and accurately locate optimal designs under any given experimental structure. For the simulation studies constructed here in Chapter 4, we adopt the optimal weight exchange algorithm (OWEA) proposed by Yang, Biedermann, and Tang (56).

4.1 The modified OWEA

The OWEA has been shown to be able to apply to a wide class of optimality problems: any set of differentiable functions of the parameters of interest; all Φ_p-optimality criteria with p being an non-negative integer; locally or multistage optimal designs. The OWEA works by iteratively updating the selected design points and their corresponding weights until convergence to a globally optimal continuous design is achieved through verification of the GET (general equivalence theorem, (28)). During this process, to optimize the weights, instead of relying completely on numeric computation, the OWEA adopts the Newton's method, a second-order optimization approach that features a quadratic convergence rate, which will increase the speed of convergence to a great extent. For various optimality targets, through applications to many commonly studied nonlinear models, in terms of convergence speed, the OWEA has been found to be consistently outperforming existing algorithms (details about the performance advantages of the OWEA can be found in (56)).

The original OWEA proposed in 2013 was implemented under locally optimal design framework and was later extended by Biedermann and Yang (in preparation) to construct a Bayesian optimal design structure. They proved the convergence of the extended OWEA and showed it to possess the qualitiy of fast computational speed under various scenarios. The extended version is similar to the original one with the main difference being the derivatives of the objective functions changed to their integration forms with respect to model parameter θ. All the other algorithm logic and procedures are similar to the original OWEA.

4.1.1 Notation and idea

The Φ_p optimality criterion embedded in the OWEA was given in Kiefer (28) and can be described using a class of functions

$$\Phi_p\left(\mathbf{\Sigma}_{\xi_0+\xi}(b)\right) = \left[\frac{1}{v}\mathrm{Tr}\left(\mathbf{\Sigma}_{\xi_0+\xi}(b)\right)^p\right]^{1/p}, \quad 0 \le p < \infty, \tag{4.1}$$

where $b(\theta)$ is the target function/parameter of interest with dimension v, and $\mathbf{\Sigma}_{\xi_0+\xi}(b) = \mathbf{V}_{\xi_0+\xi}(\hat{b})$ is the asymptotic variance of $b(\hat{\theta})$ under existing design ξ_0 and current design ξ, as defined in Equation 1.1.

Normally p here could take any non-negative integers but the following three scenarios stand out as the most commonly used criteria that have meaningful statistical interpretations.

- When $p = 0$, i.e., D-optimality that minimizes the volume of the confidence region for the parameter estimates.

$$\Phi_0\left(\mathbf{\Sigma}_{\xi_0+\xi}(b)\right) = \lim_{p\to 0}\Phi_p\left(\mathbf{\Sigma}_{\xi_0+\xi}(b)\right) = \left|\mathbf{\Sigma}_{\xi_0+\xi}(b)\right|^{1/v}.$$

- When $p = 1$, i.e., A-optimality that minimizes the sum of asymptotic variance of the estimate for each parameter dimension.

$$\Phi_1\left(\mathbf{\Sigma}_{\xi_0+\xi}(b)\right) = \frac{1}{v}\mathrm{Tr}\left(\mathbf{\Sigma}_{\xi_0+\xi}(b)\right).$$

- When $p \to \infty$, i.e., E-optimality that minimizes the maximum eigenvalue of the asymptotic variance-covariance matrix for the parameter estimates.

$$\Phi_\infty \left(\mathbf{\Sigma}_{\xi_0+\xi}(b) \right) = \lambda_{\max} \left(\mathbf{\Sigma}_{\xi_0+\xi}(b) \right).$$

Following the definition of the Φ_p criterion, its corresponding directional derivative with respect to each design point $\mathbf{x} \in \mathcal{X}$, $d_p(\mathbf{x}, \mathbf{\Sigma}_{\xi_0+\xi}(b))$, can be derived as follows,

$$d_p(\mathbf{x}, \mathbf{\Sigma}_{\xi_0+\xi}(b)) = C(\mathbf{\Sigma}_{\xi_0+\xi}(b)) \operatorname{Tr} \left((\mathbf{\Sigma}_{\xi_0+\xi}(b))^{p-1} A(\mathbf{x}, b, \xi) \right), \tag{4.2}$$

where

$$A(\mathbf{x}, b, \xi) \propto \left(\frac{\partial b(\theta)}{\partial \theta^T} \right) (\mathbf{I}_{\xi_0+\xi})^{-1} (\mathbf{I}_{\mathbf{x}} - \mathbf{I}_{\xi}) (\mathbf{I}_{\xi_0+\xi})^{-1} \left(\frac{\partial b(\theta)}{\partial \theta^T} \right),$$

and

$$C(\mathbf{\Sigma}_{\xi_0+\xi}(b)) = \begin{cases} 1, & p = 0, \\ \left(\frac{1}{v} \right)^{\frac{1}{p}} \left(\operatorname{Tr} \left(\mathbf{\Sigma}_{\xi_0+\xi}(b) \right)^p \right)^{\frac{1}{p}-1}, & p > 0. \end{cases}$$

Notice that minimizing Φ_p given in Equation 4.1 is equivalent to minimizing

$$\tilde{\Phi}_p \left(\mathbf{\Sigma}_{\xi_0+\xi}(b) \right) = \begin{cases} \log \left| \mathbf{\Sigma}_{\xi_0+\xi}(b) \right|, & p = 0, \\ \operatorname{Tr} \left(\mathbf{\Sigma}_{\xi_0+\xi}(b) \right)^p, & p > 0. \end{cases} \tag{4.3}$$

Bayesian model-averaging

All illustrated above are with respect to a single working model, where statistical practice followed ignores the ambiguity in model selection. The underlying risk with respect to over-confident statistical inferences and presumptuous decision making makes it extremely important to take account of the problem of model uncertainty. One coherent and conceptually straightforward technique to tackle it would be Bayesian model averaging (BAM) analysis, which provides a mechanism robust to model choice since it allows researchers and practitioners to form a "committee" of candidate models instead of putting extra effort on agreeing on a single "best" one.

Let Δ be any quantity of interest, such as a parameter estimator, a loss function, or the utility of a certain action, then its posterior distribution given data $\mathcal{Y}$ can be written as

$$\mathsf{P}(\Delta|\mathcal{Y}) = \sum_{m=1}^{M} \pi_m \, \mathsf{P}(\Delta|\psi_m, \mathcal{Y}),$$

where $\psi_1, ..., \psi_M$ are the M models considered. $\mathsf{P}(\Delta|\mathcal{Y})$ can be seen as a weighted summation of the posterior distribution of Δ under each candidate model ψ_m, with leverage π_m being the posterior model probability $\mathsf{P}(\psi_m|D)$, $m = 1, ..., M$. The update of π_m with new data follows

$$\mathsf{P}(\psi_m|D) \propto \mathsf{P}(\mathcal{Y}|\psi_m) \, \mathsf{P}(\psi_m),$$

where $\mathsf{P}(\psi_m)$ is the prior belief on model m with the constraint that $\sum_{m=1}^{M} \mathsf{P}(\psi_m) = 1$, and $\mathsf{P}(\mathcal{Y}|\psi_m)$ is the integrated likelihood of $\psi_m(\theta_m)$. More specifically,

$$\mathsf{P}(\mathcal{Y}|\psi_m) = \int \mathsf{P}(\theta_m|\psi_m)\,\mathsf{P}(\mathcal{Y}|\theta_m,\psi_m)\,\mathrm{d}\theta,$$

where $\mathsf{P}(\theta_m|\psi_m)$ is the prior density for θ_m under model ψ_m, and $\mathsf{P}(\mathcal{Y}|\theta_m,\psi_m)$ is the corresponding likelihood.

Consider $\hat{\Delta}_m = \mathbf{E}(\Delta|\mathcal{Y},\psi_m)$, then the posterior mean and variance of Δ were given in Hoeting, et. al. (25) as

$$\mathbf{E}(\Delta|\mathcal{Y}) = \sum_{m=1}^{M} \hat{\Delta}_m\,\mathsf{P}(\psi_m|\mathcal{Y}),$$

and

$$\mathbf{V}(\Delta|\mathcal{Y}) = \sum_{m=1}^{M} \left(\mathbf{V}(\Delta|\mathcal{Y},\psi_m) + \hat{\Delta}_m^2\right)\,\mathsf{P}(\psi_m|\mathcal{Y}) - \mathbf{E}(\Delta|\mathcal{Y})^2.$$

Madigan and Raftery (33) pointed out that averaging over the entire model set $\mathcal{M}$ in the structure illustrate above would yield better predictive ability with respect to a logarithmic scoring metric, when compared to the way of utilizing any single working model $\psi_m \in \mathcal{M}$. Empirical studies under various setups were carried out by Hoeting, et. al. (25) that showed very promising evidence to support this theoretical statement. Here in this paper, we still face the model uncertainty problem that no one can guarantee an absolute accurate dose-toxicity response curve. Therefore we absorb the BMA strategy into our dose-finding framework to

compensate for the estimation precision loss due to the unavoidable deviation from the true underlying working mechanism.

Suppose M working models under prior belief $\boldsymbol{\pi} = (\pi_1, ..., \pi_M)$ are brought into the design, with toxicity probability respectively being $\psi_m(x, \theta_m)$, $m = 1, ..., M$. For the m^{th} model, under existing design ξ_0 and current design ξ, with target parameter function $b_m(\theta_m)$, we have

$$\boldsymbol{\Sigma}_{m,\xi_0+\xi}(b_m) = \frac{\partial b_m(\theta_m)}{\partial \theta_m^T} \mathbf{I}^{-1}_{\xi_0+\xi}(\theta_m) \left(\frac{\partial b_m(\theta_m)}{\partial \theta_m^T} \right)^T.$$

Then the weighted Φ_p, d_p, and $\tilde{\Phi}_p$ values are calculated as

$$\begin{aligned}
\Phi_p(\boldsymbol{\Sigma}_{\xi_0+\xi}(b)) &= \sum_{m=1}^{M} \pi_m \Phi_p \left(\boldsymbol{\Sigma}_{m,\xi_0+\xi}(b_m) \right), \\
d_p(\mathbf{x}, \boldsymbol{\Sigma}_{\xi_0+\xi}(b)) &= \sum_{m=1}^{M} \pi_m d_p(\mathbf{x}, \boldsymbol{\Sigma}_{m,\xi_0+\xi}(b_m)), \\
\tilde{\Phi}_p \left(\boldsymbol{\Sigma}_{\xi_0+\xi}(b) \right) &= \sum_{m=1}^{M} \pi_m \tilde{\Phi}_p \left(\boldsymbol{\Sigma}_{m,\xi_0+\xi}(b_m) \right),
\end{aligned} \tag{4.4}$$

where function $\Phi_p(\boldsymbol{\Sigma})$, $d_p(\mathbf{x}, \boldsymbol{\Sigma})$, and $\tilde{\Phi}_p(\boldsymbol{\Sigma})$ are defined respectively in Equation 4.1, Equation 4.2, and Equation 4.3.

4.1.2 Implementation of the OWEA

A step-by-step procedure of implementing the (extended) OWEA in the context of dose allocation is described as follows:

(I). Given the dose set $\mathcal{D} = \{d_1, ..., d_D\}$, we start by randomly selecting s of them and assigning equal weight of $1/s$ to each dose. The support is denoted as $\mathcal{S}^{(0)}$.

(II). With $\mathcal{S}^{(t)}$ being the given support, $t = 0, 1, 2, ...$, update the current weights for design points in $\mathcal{S}^{(t)}$ to optimal weights using Newton's method. Elimination of zero, one, or multiple design points from $\mathcal{S}^{(t)}$ may occur during Newton's iterations. $\mathcal{S}^{(t)}$ with its optimal weight $\omega^{(t)}$ constitute design $\xi^{(t)}$, $t = 0, 1, ...$

(III). For the current design $\xi^{(t)}$, find $d^* \in \mathcal{D}$ such that d^* maximizes $d_p\left(\mathbf{x}, \mathbf{\Sigma}_{\xi_0+\xi^{(t)}}(b)\right)$ (Equation 4.4). Check to see whether the value of $d_p\left(d^*, \mathbf{\Sigma}_{\xi_0+\xi^{(t)}}(b)\right)$ is less than ϵ, a pre-specified threshold. If so, $\xi^{(t)}$ is the desired design, i.e., the optimal dose allocation for the newly recruited cohort of patients. Otherwise, go to the next step.

(IV). Update $\xi^{(t)}$ by including d^* with weight zero. Then we have a new support $\mathcal{S}^{(t+1)} = \{\mathcal{S}^{(t)}, d^*\}$ with initial weight $\{\omega^{(t)}, 0\}$ to repeat steps (II) and (III).

Remark 2. *The choice of s in step (I) does not matter that much in theory since different resulting continuous optimal designs from different starting designs should all be equivalent in the sense that they all have the same objective criterion value. But we need to mention that the increase of s will cause the increase of difficulty in computing the Hessian matrix embedded in Newton's method, thus slow down the computation speed. Here we recommend selecting three doses to begin with, i.e., $s = 3$, one low dose, one high dose, and one from the middle.*

Remark 3. *The rationale behind step (III) lies within the theory of the GET, where a design ξ^* is Φ_p-optimal for $b(\theta)$ if and only if for all $\mathbf{x} \in \mathcal{X}$, we have*

$$d_p(\mathbf{x}, \xi^*) = \frac{\partial \Phi_p\left(\mathbf{\Sigma}_{\xi_0+\xi^*}(b)\right)}{\partial \mathbf{x}} \leq 0,$$

with equality achieved only at $\mathbf{x} \in \xi^*$.

The Newton's method in step (II) can be performed according to the following steps (start with $\alpha = 1$):

(i). With support $\mathcal{S}^{(t)}$ and current weight at the r^{th} iteration $\omega_r^{(t)}$, $r = 0, 1, 2, ...$, $t = 0, 1, 2, ...$, next iteration updates $\omega_r^{(t)}$ by

$$\omega_{r+1}^{(t)} = \omega_r^{(t)} - \alpha \left(\frac{\partial^2 \tilde{\Phi}_p \left(\mathbf{\Sigma}_{\xi_0 + \xi^{(t)}}(b) \right)}{\partial \omega \partial \omega^T} \bigg|_{\omega = \omega_r^{(t)}} \right)^{-1} \frac{\partial \tilde{\Phi}_p \left(\mathbf{\Sigma}_{\xi_0 + \xi^{(t)}}(b) \right)}{\partial \omega} \bigg|_{\omega = \omega_r^{(t)}},$$

where $\xi^{(t)}$ denotes design with support $\mathcal{S}^{(t)}$ and weight to be determined, and the model-averaged function $\tilde{\Phi}_p(\mathbf{\Sigma})$ is defined in Equation 4.4.

(ii). Check to see if there are non-positive components in $\omega_{r+1}^{(t)}$. If so, go to step (iv); otherwise, go to step (iii).

(iii). Check if $\left\| \frac{\partial \tilde{\Phi}_p \left(\mathbf{\Sigma}_{\xi_0 + \xi^{(t)}}(b) \right)}{\partial \omega} \bigg|_{\omega = \omega_{r+1}^{(t)}} \right\|$, where $||\cdot||$ denotes the Euclidean norm, is less than ϵ', another predetermined cutoff. If so, $\omega_{r+1}^{(t)}$ is the desired/optimal weight for support $\mathcal{S}^{(t)}$. Otherwise, start the next iteration.

(iv). Reduce α by half, repeat step (i) until α reaches ϵ'', also a pre-specified limit. Then remove the sample point/dose level with the smallest weight; reset α to 1 and go back to step (i) with the new support and its corresponding weight.

Remark 4. *The three thresholds,* ϵ, ϵ', *and* ϵ'', *were set to be* 10^{-6} *in the empirical study.*

The model-averaged derivatives, $\frac{\partial\tilde{\Phi}_p\left(\mathbf{\Sigma}_{\xi_0+\xi}(b)\right)}{\partial\omega}$ and $\frac{\partial^2\tilde{\Phi}_p\left(\mathbf{\Sigma}_{\xi_0+\xi}(b)\right)}{\partial\omega\partial\omega^T}$, following Equation 4.4, are described below:

$$\frac{\partial\tilde{\Phi}_p\left(\mathbf{\Sigma}_{\xi_0+\xi}(b)\right)}{\partial\omega} = \sum_{m=1}^{M}\pi_m\frac{\partial\tilde{\Phi}_p\left(\mathbf{\Sigma}_{m,\xi_0+\xi}(b_m)\right)}{\partial\omega},$$
$$\frac{\partial^2\tilde{\Phi}_p\left(\mathbf{\Sigma}_{\xi_0+\xi}(b)\right)}{\partial\omega\partial\omega^T} = \sum_{m=1}^{M}\pi_m\frac{\partial^2\tilde{\Phi}_p\left(\mathbf{\Sigma}_{m,\xi_0+\xi}(b_m)\right)}{\partial\omega\partial\omega^T},$$

where for the m^{th} model, $m = 1, ..., M$, $\tilde{\Phi}_p\left(\mathbf{\Sigma}_{m,\xi_0+\xi}(b_m)\right)$ is given in Equation 4.3. Concrete expressions of $\frac{\partial\tilde{\Phi}_p\left(\mathbf{\Sigma}_{m,\xi_0+\xi}(b_m)\right)}{\partial\omega}$ and $\frac{\partial^2\tilde{\Phi}_p\left(\mathbf{\Sigma}_{m,\xi_0+\xi}(b_m)\right)}{\partial\omega\partial\omega^T}$ can be found in (56).

4.2 Weight function update

In the work of Cheung and Chappell (8), the authors assumed that the weight function is linear and increasing with respect to the enrollment time. Applying this idea, the time-weighted estimate for the weight function, for $k = 0, 1, ..., K$, follows

$$\tilde{w}_k = \frac{u_k}{T}.$$

Ji and Bekele (26) pointed out that when the assumption of linearity is violated, the time-weighted method may lead to biased results. Similar to their model-based approach, we describe here a Bayesian method to estimate the weight function.

At a certain interim study time point, we have $n^{tox} := \sum_{k=1}^{K} n^{tox_k}$ patients who have experienced DLT, where for each k, n^{tox_k} is the number of patients whose toxicity reaction showed up in time interval $(u_{k-1}, u_k]$. Notice that here the time points and time intervals are regarding

the timeline of each individual patient, instead of the whole trial. Then of all the n^{tox} patients, those whose DLT occur before enrollment time u_k can be calculated as $\sum_{l=1}^{k} n^{tox_l}$, which is related with the time-to-toxicity with respect to each dose level. Since at any study point, given the current observed data, n^{tox} is fixed; thus conditioned on n^{tox}, for each $k = 1, ..., K$, we have

$$\sum_{l=1}^{k} n^{tox_l} \sim \text{Binom}(n^{tox}, w_k).$$

Assume the prior for w_k follows $\text{Beta}(\alpha_k^{(0)}, \beta_k^{(0)})$, where $\alpha_k^{(0)}, \beta_k^{(0)} > 0$ are the shape parameters. The elicitation of $\alpha_k^{(0)}$ and $\beta_k^{(0)}$ could follow the relation

$$\mathbf{E}(\text{Beta}(\alpha_k^{(0)}, \beta_k^{(0)})) = \frac{\alpha_k^{(0)}}{\alpha_k^{(0)} + \beta_k^{(0)}} \stackrel{set}{=} \tilde{w}_k = \frac{u_k}{T} \tag{4.5}$$

so that the prior is centered about the time-weighted estimate $\tilde{w}_k$ introduced above. Taking advantage of conjugacy between Binomial and Beta distribution, we have the posterior of w_k following

$$w_k \sim \text{Beta}\left(\alpha_k^{(0)} + \sum_{l=1}^{k} n^{tox_l}, \beta_k^{(0)} + n^{tox} - \sum_{l=1}^{k} n^{tox_l}\right),$$

which effectively, can be viewed as adding $\alpha_k^{(0)} - 1$ toxicities and $\beta_k^{(0)} - 1$ non-toxicities to the data set. Then after achieving the posterior distribution, the estimate $\hat{w}_k$, $k = 1, 2, ..., K$, can be obtained via posterior mean:

$$\hat{w}_k = \frac{\alpha_k^{(0)} + \sum_{l=1}^{k} n^{tox_l}}{\alpha_k^{(0)} + \beta_k^{(0)} + n^{tox}}.$$

4.3 Algorithm for the OD-CRM

Now we illustrate the procedures for carrying out the OD-CRM.

(I). Calculate respectively the prior mean for weight function $\boldsymbol{w} = (w_1, ..., w_K)$ from the prior Beta distribution stated in Equation 4.5, and for model parameters $\boldsymbol{\theta} = (\theta_1, ..., \theta_M)$ from each corresponding prior distributions $g_m^{(0)}(\theta_m)$, $m = 1, ..., M$. Denote them as $\boldsymbol{w}^{(0)}$ and $\boldsymbol{\theta}^{(0)}$. Assume a model prior for model averaging scheme, $\boldsymbol{\pi}^{(0)} = (\pi_1^{(0)}, ..., \pi_M^{(0)})$. Then apply the OWEA illustrated in Section 4.1.2 to obtain the optimal dose allocation $\xi^{(1)} \left| \left(\boldsymbol{w}^{(0)}, \boldsymbol{\theta}^{(0)}, \boldsymbol{\pi}^{(0)} \right) \right.$ for the first entered cohort.

(II). Before the $r+1^{\text{th}}$ recruitment, $r = 1, 2, ..., R-1$, with R being the preset cohort limit, the observed toxicity response, enrollment time, and time-to-toxicity with respect to each enrolled patient are recorded in data set $\mathcal{Z}^{(r)}$. We then update the posterior distribution and estimate for $\boldsymbol{w}$, $\boldsymbol{\theta}$, and $\boldsymbol{\pi}$ under Bayesian structure:

(i) Regarding the weight function, for $k = 1, ..., K$, we have

$$w_k^{(r)} \sim \text{Beta}\left(\alpha_k^{(0)} + \sum_{l=1}^{k} \left(n^{tox_l} \left| \mathcal{Z}^{(r)} \right. \right), \beta_k^{(0)} + \left(n^{tox} \left| \mathcal{Z}^{(r)} \right. \right) - \sum_{l=1}^{k} \left(n^{tox_l} \left| \mathcal{Z}^{(r)} \right. \right) \right),$$

and

$$w_k^{(r)} = \frac{\alpha_k^{(0)} + \sum_{l=1}^{k} \left(n^{tox_l} \left| \mathcal{Z}^{(r)} \right. \right)}{\alpha_k^{(0)} + \beta_k^{(0)} + \left(n^{tox} \left| \mathcal{Z}^{(r)} \right. \right)},$$

where $\alpha_k^{(0)}$ and $\beta_k^{(0)}$ are chosen based on the elicitation rule stated in Equation 4.5.

Remark 5. *In the empirical study, for each k we set $\alpha_k^{(0)} = u_k$, $\beta_k^{(0)} = T - u_k$.*

(ii) Regarding the model parameter, for $m = 1, ..., M$, we have

$$g_m^{(r)}(\theta_m) \propto g_m^{(0)}(\theta_m) \cdot L_m\left(\theta_m \middle| \mathcal{Z}^{(r)}\right), \tag{4.6}$$

and

$$\theta_m^{(r)} = \int \theta_m \cdot g_m^{(r)}(\theta_m)\, \mathrm{d}\theta_m,$$

where likelihood function $L_m(\theta_m)$ is given in Equation 3.15. Notice that here for different models, the p, q functions, involved in the likelihood and defined in Equation 1.2 and Equation 1.3, are also different due to the change in toxicity probability model $\psi_m(x, \theta_m)$.

(iii) Regarding the model weights, for $m = 1, ..., M$, we have two ways for updating, where we either use the posterior mean for each θ_m, or use the posterior distribution.

- Posterior mean.

$$\pi_m^{(r)}\left|\theta_m^{(r)}\right. \propto \pi_m^{(0)} \cdot L_m\left(\theta_m^{(r)}\right).$$

- Posterior distribution.

$$\pi_m^{(r)}\left|g_m^{(r)}\right. \propto \pi_m^{(0)} \cdot \int L_m\left(\theta_m \middle| \mathcal{Z}^{(r)}\right) \cdot g_m^{(r)}(\theta_m)\, \mathrm{d}\theta_m.$$

(III). Optimal dose allocation $\xi^{(r+1)}\left|\left(\boldsymbol{w}^{(r)}, \boldsymbol{\theta}^{(r)}, \boldsymbol{\pi}^{(r)}\right)\right.$ is constructed for the $(r+1)^{\text{th}}$ entered cohort, $r = 1, ..., R-1$. Then repeat step (II) until maximum sample size is reached.

For those in the study without being fully evaluated, we follow them until every one of them has completed the entire assessment period T.

(IV). Final inference regarding the MTD is made based on the complete data $\mathcal{Z}^{(R)}$. Due to the estimation method difference lie in the $\boldsymbol{\pi}$ update, we have two final estimates for toxicity probability p_d, for each $d \in \mathcal{D}$.

- Posterior Mean.

$$\hat{p}_d \left| \boldsymbol{\theta}^{(R)} \right. = \sum_{m=1}^{M} \left(\pi_m^{(R)} \left| \theta_m^{(R)} \right. \right) \cdot \psi_m \left(d, \theta_m^{(R)} \right).$$

- Posterior distribution.

$$\hat{p}_d \left| \boldsymbol{g}^{(R)} \right. = \sum_{m=1}^{M} \left(\pi_m^{(R)} \left| g_m^{(R)} \right. \right) \cdot \int \psi_m(d, \theta_m) \cdot g_m^{(R)}(\theta_m) \, \mathrm{d}\theta_m.$$

Then Final MTD estimation, d^*, is given by

$$d^* = \min_{d \in \mathcal{D}} |\hat{p}_d - p_t|$$

where p_t is the pre-determined target toxicity rate.

We should mention that although under Bayesian structure, our posterior update for $\boldsymbol{w}$, $\boldsymbol{\theta}$, and $\boldsymbol{\pi}$ are all based on current cumulative likelihood $L^{(r)}$ and their start-up priors, instead of the standard approach where the posterior from the last iteration is adopted as the prior for

the next update, these two methods are actually equivalent to each other. We shall roughly explained it here.

Under standard Bayesian framework, with an assumed start-up prior $f^{(0)}$, after the r^{th} observation(s), the posterior distribution for the model parameter is updated following

$$f^{(r)} \propto L\left(\mathcal{Y}^{(r)}\right) \cdot L\left(\mathcal{Y}^{(r-1)}\right) \cdots L\left(\mathcal{Y}^{(1)}\right) \cdot f^{(0)},$$

where $\mathcal{Y}^{(r)}$ denotes the data change after the inclusion of the r^{th} subject(s). When applied in the clinical trial situation, we have $\mathcal{Y}^{(r)} = \mathcal{Z}^{(r)} \setminus \mathcal{Z}^{(r-1)}$, which stems from the fact that the recorded response $\mathcal{Z}^{(r)}$ here in the dose-finding study with late-onset toxicities, is the multinomial data showing the patients' accumulative DLT experiences after the enrollment of the r^{th} cohort (see Equation 3.14), instead of the observation change occurred in between of the post-recruitment of the $(r-1)^{\text{th}}$ and r^{th} cohort. Therefore we have

$$\begin{aligned}
f^{(r)} &\propto L\left(\mathcal{Y}^{(r)}\right) \cdot L\left(\mathcal{Y}^{(r-1)}\right) \cdots L\left(\mathcal{Y}^{(1)}\right) \cdot f^{(0)} \\
&= L\left(\mathcal{Z}^{(r)} \setminus \mathcal{Z}^{(r-1)}\right) \cdot L\left(\mathcal{Z}^{(r-1)} \setminus \mathcal{Z}^{(r-2)}\right) \cdots L\left(\mathcal{Z}^{(1)} \setminus \mathcal{Z}^{(0)}\right) \cdot f^{(0)} \\
&= L\left(\left(\mathcal{Z}^{(r)} \setminus \mathcal{Z}^{(r-1)}\right) \cup \left(\mathcal{Z}^{(r-1)} \setminus \mathcal{Z}^{(r-2)}\right) \cup \left(\mathcal{Z}^{(1)} \setminus \mathcal{Z}^{(0)}\right)\right) \cdot f^{(0)} \\
&\overset{\mathcal{Z}^{(0)}=\emptyset}{=\!=\!=} L\left(\mathcal{Z}^{(r)}\right) \cdot f^{(0)}.
\end{aligned}$$

Compared with Equation 4.6, we can see that they are in fact the same.

4.4 Empirical study

Here in this section we compare the performance of the proposed OD-CRM with three previously established methods reviewed in Chapter 2, i.e., the TITE-CRM, the EM-CRM, and the DA-CRM. Notation regarding different designs are listed below.

- OD_{MEAN}: OD-CRM coupled with the posterior mean structure;
- OD_{BAYE}: OD-CRM coupled with the posterior distribution structure;
- $\text{TITE}_{\text{MEAN}}$: TITE-CRM without the initial stage and θ is updated with its posterior mean at each step;
- TITE_{MLE}: TITE-CRM with the initial stage and after switching to the standard TITE design, θ is updated with its MLE at each step;
- EM_{SEL}: EM-CRM coupled with the model selection analysis;
- EM_{AVG}: EM-CRM coupled with the model averaging analysis;
- DA: the standard DA-CRM.

All the algorithms are implemented following their implementation procedures respectively given in Section 2.1, 2.2, 2.3, and 4.3. One thing we mention here is that, for the BMA technique we built into the OD-CRM designs, when considering the power model, instead of focusing on a single selected skeleton, we use three of them the same as mentioned in the EM-CRM design. They share the same parameter α_p and are equally weighted. That is, the weight for each skeleton/each power model stay the same through the whole the trial with summation equal

to π_1, the total power model weight. The rest analysis follows the exact same structure as explained under the BMA framework.

Data generating mechanism	Toxicity scenarios
Model averaging with $\alpha_p = 0.5$, $\theta_l = (-3, 1.5)$, $\theta_{pb} = (-2.5, 0.5)$, $\mathbf{w} = \{0.3, 0.4, 0.3\}$	0.10, 0.15, 0.20, 0.30, 0.50, 0.70
	0.05, 0.10, 0.15, 0.20, 0.27, 0.35
	0.05, 0.10, 0.15, 0.20, 0.25, 0.30
	0.25, 0.32, 0.40, 0.50, 0.60, 0.70
	0.30, 0.40, 0.50, 0.55, 0.60, 0.70
	0.02, 0.05, 0.08, 0.30, 0.40, 0.50
	0.20, 0.25, 0.30, 0.35, 0.40, 0.45
Power model with $\alpha_p = 0.5$	0.10, 0.15, 0.20, 0.30, 0.50, 0.70
Logistic model with $\theta_l = (-3, 1.5)$	0.10, 0.15, 0.20, 0.30, 0.50, 0.70
Probit model with $\theta_{pb} = (-2.5, 0.5)$	0.10, 0.15, 0.20, 0.30, 0.50, 0.70
Non-parametric with dose set $\{1, 2, 3, 4, 5, 6\}$	0.10, 0.15, 0.20, 0.30, 0.50, 0.70

Table 12: Toxicity configurations in the comparison of difference designs

Six dose levels were involved in all scenarios with eleven toxicity configurations listed in Table 12. The first seven were generated by an averaged model that included all the three models we referred to earlier, with model parameters and model weights specified in the first column. The latter three were designed for the situations when we assume the toxicity response is induced by a single working model. And the very last scenario pointed to the set-

ting of an non-parametric case with monotone dose-toxicity constraint implied. When power model was involved in toxicity generation, the skeleton of the dose set (toxicity belief of each dose level) is computed with formula $\frac{\exp(x)}{\exp(x)+1}$, where x is the corresponding dose level. This simulated skeleton-dose curve gave us a standard increasing relationship which we believe can represent a non-knowledgeable prior view of the toxic character of different dose levels with no other medical or clinical information interfering. Note that under the same data generating mechanism, different toxicity scenarios imply different dose sets. For example, the dose sets for scenario 1 and 2, respectively, are $\mathcal{D}_1 = \{1.08, 1.43, 1.70, 2.17, 3.06, 4.09\}$ and $\mathcal{D}_2 = \{0.54, 1.08, 1.43, 1.70, 2.04, 2.39\}$. And for the case when the toxicity configurations are the same, different working models would mean different dose sets. For example, the dose sets for scenario 9 and 10, respectively, are $\mathcal{D}_9 = \{0.54, 0.84, 1.08, 1.44, 2.00, 2.56\}$ and $\mathcal{D}_{10} = \{2.44, 2.93, 3.32, 3.95, 5.00, 6.05\}$.

Now we present the reasons for choosing these eleven toxicity configurations. The first one is a general demonstration of one's belief on the toxicity rate distribution that is well-spread across the range of the dose set and at the same time, approximately equally-spaced with the target one fitted in the middle. The second and the third were constructed within a conservative view where all six doses produce relatively low toxicity rate and the target rate is thus pushed to the end. The forth and fifth were presented as contrasts to the previous pair in the sense that now doses were assumed to be over-toxic such that the target rate shows up by the beginning. Note that the second and fourth scenarios did not contain the target 0.3, thus the nearest, i.e., 0.27 and 0.32 were considered the "right" toxicity to choose, respectively. These two were meant to

simulate the situation where an exact target dose is not part of the pre-determined available set that study is built on. The sixth scenario has a jump in the probabilities, that is, the first three rates are all under 0.1 and then leaps to the target, 0.3, at the forth dose. The seventh was sketched with the six toxicity rates very close to each other so that it would be more difficult for the algorithms to distinguish from one another. And the following three scenarios were included here to show the advantage of using BMA analysis when the assumed single working model in the design is actually wrong. The very last one gives us some perspective into the doubt that whether model-based designs can perform well when they are forced to cope with an non-parametric generating mechanism.

Sample size was set at 48 with cohort size 4, thus we have a total of 12 recruitments. For the OD-CRM designs, the unknown model parameter was targeted at the first 6 recruitments, i.e., optimal designs were built for θ, in order to obtain better θ inferences; then the MTD took over as the parameter of interest during the last 6 recruitments, i.e.,optimal designs were built for the MTD, aiming to produce more accurate MTD recommendations. The evaluation period was 12 month ($T = 12$) with enrollment took place at the 1st, 2nd, 4th, 6th, 8.5th, and the 12th month, that is, we have a total of 7 ($K = 7$) interim study time point with each u_k settled up as described. The true weight function $\mathbf{w} = \{w_1, ..., w_7\}$ that helped generating data was placed at $\mathbf{w} = \{0.15, 0.28, 0.45, 0.59, 0.71, 0.92, 1.00\}$. Target toxicity rate was set to be 30% ($p_t = 0.3$). BMA technique involving all three models was utilized through all OD-CRM designs with model prior $\{1/3, 1/3, 1/3\}$. Simulation results are presented in Table 13.

The entries consist of a pair of number show the simulation results of each design under each scenario where, at each dose, the 1st number is the percentage of recommendation for the MTD and the 2nd is the percentage of patients treated there. Last column of the table is the percentage of patients experiencing DLTs.

Design	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	DLT percentage
Scenario 1	0.10	0.15	0.20	**0.30**	0.50	0.70	
OD_{MEAN}	(0.00,45.27)	(3.20,8.42)	(22.80,6.10)	**(68.00,10.45)**	(6.00,13.40)	(0.00,16.36)	28.47
OD_{BAYE}	(0.20,41.86)	(4.60,23.00)	(26.00,6.44)	**(59.20,2.73)**	(9.60,12.55)	(0.40,13.42)	25.59
$TITE_{MEAN}$	(0.00,9.08)	(4.60,16.00)	(28.20,26.33)	**(60.40,41.12)**	(6.80,6.90)	(0.00,0.57)	24.81
$TITE_{MLE}$	(0.20,17.12)	(6.60,27.07)	(33.00,27.15)	**(54.40,22.57)**	(5.80,5.75)	(0.00,0.35)	21.00
EM_{SEL}	(0.00,18.92)	(5.20,22.12)	(33.40,21.57)	**(48.20,16.43)**	(12.40,11.98)	(0.80,8.98)	26.81
EM_{AVG}	(0.00,20.92)	(4.40,21.67)	(32.20,18.87)	**(51.80,19.90)**	(11.60,11.93)	(0.00,6.72)	25.59
DA	(0.00,44.83)	(0.00,34.67)	(3.00,17.00)	**(58.20,2.75)**	(32.00,0.33)	(6.80,0.42)	30.52
Scenario 2	0.05	0.10	0.15	0.20	**0.27**	0.35	
OD_{MEAN}	(0.00,24.16)	(0.20,7.35)	(2.40,5.52)	(14.60,4.28)	**(48.20,3.65)**	(34.60,55.04)	23.80
OD_{BAYE}	(0.00,19.93)	(0.40,17.96)	(5.60,10.93)	(23.40,7.09)	**(41.20,4.54)**	(29.40,39.55)	20.67
$TITE_{MEAN}$	(0.00,0.33)	(0.00,7.83)	(3.00,18.42)	(44.60,46.87)	**(49.80,21.37)**	(2.60,0.22)	19.33
$TITE_{MLE}$	(0.00,10.62)	(0.20,17.53)	(7.00,22.28)	(44.60,30.53)	**(40.40,15.33)**	(7.80,3.70)	17.15

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Design	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	DLT percentage
EM_{SEL}	(0.00,11.23)	(0.00,13.87)	(3.80,14.80)	(18.60,14.48)	**(33.40,15.13)**	(44.20,30.48)	21.65
EM_{AVG}	(0.00,12.42)	(0.00,14.50)	(3.00,13.85)	(29.80,19.75)	**(41.80,17.17)**	(35.40,22.32)	20.53
DA	(0.00,11.00)	(0.00,14.42)	(7.60,20.08)	(31.40,26.67)	**(35.00,18.67)**	(26.00,9.17)	19.17
Scenario 3	0.05	0.10	0.15	0.20	0.25	**0.30**	
OD_{MEAN}	(0.00,25.98)	(0.00,5.08)	(1.80,3.77)	(11.20,3.82)	(18.60,2.45)	**(68.40,58.90)**	21.15
OD_{BAYE}	(0.00,23.74)	(0.40,6.77)	(5.40,15.37)	(20.40,9.89)	(25.20,6.72)	**(48.60,37.52)**	19.12
$TITE_{MEAN}$	(0.00,2.97)	(0.00,7.48)	(5.00,16.58)	(29.00,46.62)	(40.20,23.27)	**(25.80,3.08)**	19.04
$TITE_{MLE}$	(0.00,10.30)	(0.40,15.87)	(6.00,22.85)	(33.00,29.78)	(30.40,16.37)	**(30.20,4.83)**	16.60
EM_{SEL}	(0.00,12.22)	(0.00,14.65)	(4.00,13.50)	(14.42,14.12)	(30.20,13.68)	**(51.60,31.83)**	19.91
EM_{AVG}	(0.00,12.48)	(0.40,13.72)	(5.40,14.98)	(16.00,18.30)	(33.60,15.38)	**(44.60,25.13)**	19.46
DA	(0.00,9.58)	(0.00,15.08)	(2.80,19.17)	(28.20,25.75)	(32.40,16.92)	**(36.60,13.50)**	18.17
Scenario 4	0.20	**0.30**	0.40	0.50	0.60	0.70	
OD_{MEAN}	(35.20,70.55)	**(48.20,2.01)**	(15.20,7.43)	(1.40,2.33)	(0.00,8.05)	(0.00,9.64)	34.43
OD_{BAYE}	(39.20,73.32)	**(46.80,6.84)**	(12.60,4.48)	(1.40,1.92)	(0.00,0.52)	(0.00,8.28)	32.18

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Design	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	DLT percentage
$\text{TITE}_{\text{MEAN}}$	(34.80,42.75)	**(48.00,23.97)**	(16.00,11.77)	(1.20,19.92)	(0.00,1.55)	(0.00,0.05)	34.12
TITE_{MLE}	(39.20,58.42)	**(46.80,29.18)**	(13.20,9.68)	(0.80,0.25)	(0.00,0.22)	(0.00,0.00)	28.80
EM_{SEL}	(46.40,59.30)	**(37.60,25.18)**	(14.40,8.97)	(1.60,4.17)	(0.00,1.80)	(0.00,0.58)	30.15
EM_{AVG}	(45.00,63.15)	**(39.20,22.17)**	(14.60,9.48)	(1.00,3.93)	(0.20,0.98)	(0.00,0.28)	29.63
DA	(0.20,47.33)	**(40.20,31.17)**	(54.60,16.42)	(3.20,5.00)	(0.00,0.08)	(0.00,0.00)	29.96
Scenario 5	**0.30**	0.40	0.50	0.55	0.60	0.70	
OD_{MEAN}	**(69.00,72.34)**	(23.60,2.28)	(6.80,7.70)	(0.60,1.94)	(0.00,7.83)	(0.00,7.91)	37.88
OD_{BAYE}	**(73.40,76.46)**	(23.80,6.78)	(2.40,4.06)	(0.40,1.78)	(0.00,5.18)	(0.00,5.75)	35.97
$\text{TITE}_{\text{MEAN}}$	**(62.20,54.13)**	(33.80,19.58)	(4.00,6.95)	(0.00,18.02)	(0.00,1.30)	(0.00,0.02)	37.64
TITE_{MLE}	**(73.20,75.07)**	(25.00,19.67)	(1.80,4.40)	(0.00,0.82)	(0.00,0.05)	(0.00,0.00)	33.05
EM_{SEL}	**(74.80,72.20)**	(22.40,19.20)	(2.40,5.43)	(0.40,1.93)	(0.00,0.82)	(0.00,0.42)	33.16
EM_{AVG}	**(77.60,77.83)**	(19.60,15.52)	(2.60,4.52)	(0.20,1.65)	(0.00,0.37)	(0.00,0.12)	33.23
DA	**(45.80,61.67)**	(50.00,28.25)	(3.00,9.33)	(1.20,0.75)	(0.00,0.00)	(0.00,0.00)	35.52
Scenario 6	0.02	0.05	0.08	**0.30**	0.40	0.50	

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Design	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	DLT percentage
OD_{MEAN}	(0.00,38.17)	(1.40,5.44)	(29.60,5.38)	(**54.20,3.53**)	(14.80,9.72)	(0.00,37.78)	25.41
OD_{BAYE}	(0.00,25.13)	(0.60,16.67)	(23.60,18.33)	**(58.80,13.80)**	(17.00,7.12)	(0.00,18.95)	18.76
$TITE_{MEAN}$	(0.00,5.33)	(0.00,11.80)	(21.80,21.58)	**(59.20,49.88)**	(19.00,10.78)	(0.00,0.62)	21.82
$TITE_{MLE}$	(0.00,8.70)	(0.00,10.72)	(32.60,19.00)	**(57.00,40.18)**	(9.40,19.65)	(1.00,1.75)	22.78
EM_{SEL}	(0.00,9.63)	(3.00,10.71)	(42.00,13.54)	**(48.00,20.67)**	(7.00,17.58)	(0.00,27.88)	28.60
EM_{AVG}	(0.00,10.42)	(3.00,11.17)	(47.50,13.33)	**(45.50,23.92)**	(4.00,23.54)	(0.00,17.63)	27.13
DA	(0.00,9.67)	(6.20,11.92)	(56.20,15.75)	**(35.60,27.75)**	(2.00,25.25)	(0.00,9.67)	25.38
Scenario 7	0.20	0.25	**0.30**	0.35	0.40	0.45	
OD_{MEAN}	(10.80,57.95)	(27.00,1.83)	(**30.80,2.16**)	(18.40,2.32)	(8.00,1.18)	(5.00,34.56)	29.60
OD_{BAYE}	(12.60,57.13)	(38.60,11.88)	**(33.20,4.21)**	(11.80,1.66)	(2.60,0.31)	(1.20,24.82)	27.47
$TITE_{MEAN}$	(3.00,18.47)	(30.20,23.68)	**(40.80,21.85)**	(23.80,31.23)	(2.20,4.48)	(0.00,0.28)	28.88
$TITE_{MLE}$	(14.20,42.47)	(41.60,30.98)	**(30.60,17.20)**	(13.00,8.67)	(0.60,0.58)	(0.00,0.10)	24.95
EM_{SEL}	(18.80,42.57)	(30.40,27.97)	**(27.00,13.53)**	(13.80,7.37)	(9.00,4.27)	(1.00,4.30)	25.91
EM_{AVG}	(17.40,47.98)	(37.00,23.58)	**(25.00,13.65)**	(14.20,8.50)	(6.00,3.68)	(0.40,0.26)	25.44

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Design	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	DLT percentage
DA	(0.00,34.83)	(1.00,29.58)	**(35.20,21.33)**	(49.20,0.11)	(12.60,2.75)	(2.00,0.42)	26.40
Scenario 8	0.10	0.15	0.20	**0.30**	0.50	0.70	
OD_{MEAN}	(0.60,55.31)	(15.40,6.27)	(20.80,8.99)	**(58.40,2.98)**	(4.60,6.34)	(0.20,20.11)	27.46
OD_{BAYE}	(0.40,50.08)	(11.60,14.00)	(33.80,14.87)	**(47.00,1.60)**	(7.20,4.17)	(0.00,15.28)	25.61
$TITE_{MEAN}$	(0.00,15.90)	(9.60,23.48)	(24.80,29.07)	**(65.40,28.27)**	(0.20,3.13)	(0.00,0.15)	26.92
$TITE_{MLE}$	(0.20,16.43)	(11.60,30.80)	(25.60,33.85)	**(62.20,17.25)**	(0.40,1.60)	(0.00,0.07)	24.59
EM_{SEL}	(0.80,18.63)	(11.60,25.23)	(31.00,23.17)	**(50.80,16.07)**	(5.60,10.15)	(0.20,6.80)	28.52
EM_{AVG}	(0.40,22.63)	(12.00,23.63)	(28.40,24.47)	**(55.20,17.95)**	(4.00,7.47)	(0.00,3.85)	26.96
DA	(0.00,16.25)	(2.40,21.88)	(27.00,28.21)	**(59.40,24.33)**	(11.20,7.96)	(0.00,1.38)	23.57
Scenario 9	0.10	0.15	0.20	**0.30**	0.50	0.70	
OD_{MEAN}	(0.00,36.84)	(10.80,24.99)	(36.20,9.39)	**(49.60,6.74)**	(3.40,3.56)	(0.00,18.48)	25.63
OD_{BAYE}	(0.00,38.39)	(9.60,23.08)	(34.60,15.21)	**(52.00,7.55)**	(3.80,0.20)	(0.00,15.57)	24.60
$TITE_{MEAN}$	(0.00,16.72)	(9.60,24.20)	(40.40,26.90)	**(49.80,28.33)**	(0.20,3.63)	(0.00,0.22)	26.85
$TITE_{MLE}$	(0.00,16.48)	(9.40,30.83)	(45.00,32.12)	**(44.00,17.90)**	(1.60,2.63)	(0.00,0.03)	24.64

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Design	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	DLT percentage
EM_{SEL}	(0.00,21.38)	(12.20,23.65)	(41.40,26.15)	**(44.40,17.95)**	(2.00,7.47)	(0.00,3.40)	26.66
EM_{AVG}	(0.00,19.48)	(13.00,26.68)	(39.40,23.67)	**(41.40,15.15)**	(6.00,9.35)	(0.20,5.67)	27.84
DA	(0.00,17.92)	(5.00,24.67)	(32.60,27.58)	**(56.40,22.83)**	(6.00,5.67)	(0.00,1.33)	22.67
Scenario 10	0.10	0.15	0.20	**0.30**	0.50	0.70	
OD_{MEAN}	(0.00,48.23)	(19.00,6.40)	(30.20,9.31)	**(48.60,6.89)**	(2.20,8.33)	(0.00,20.84)	29.63
OD_{BAYE}	(0.00,44.63)	(11.00,12.23)	(35.80,18.48)	**(47.80,7.50)**	(5.20,0.84)	(0.20,16.31)	26.14
$TITE_{MEAN}$	(0.00,17.52)	(0.20,23.57)	(8.40,27.47)	**(68.20,27.92)**	(23.20,3.35)	(0.00,0.18)	27.04
$TITE_{MLE}$	(0.00,16.70)	(10.00,30.95)	(43.20,30.75)	**(45.40,18.87)**	(1.40,2.65)	(0.00,0.08)	24.58
EM_{SEL}	(0.00,16.72)	(11.20,25.35)	(44.00,24.40)	**(38.60,15.97)**	(6.00,10.75)	(0.20,6.82)	29.17
EM_{AVG}	(0.20,20.02)	(11.00,23.95)	(44.40,24.95)	**(41.20,20.17)**	(3.20,7.68)	(0.00,3.23)	27.22
DA	(0.00,12.83)	(0.40,20.42)	(27.40,26.83)	**(57.20,26.58)**	(15.00,10.00)	(0.00,3.33)	23.81
Scenario 11	0.10	0.15	0.20	**0.30**	0.50	0.70	
OD_{MEAN}	(0.00,37.65)	(12.00,20.22)	(41.20,14.10)	**(45.40,7.24)**	(1.40,8.70)	(0.00,12.08)	25.96
OD_{BAYE}	(0.40,37.46)	(11.20,17.55)	(45.40,15.34)	**(40.60,14.59)**	(2.40,7.02)	(0.00,8.03)	26.05

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Design	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	DLT percentage
$\text{TITE}_{\text{MEAN}}$	(0.20,17.04)	(5.60,23.83)	(35.60,27.29)	**(46.80,28.51)**	(11.60,3.18)	(0.20,0.15)	26.95
TITE_{MLE}	(0.00,17.13)	(12.00,31.40)	(42.00,31.62)	**(44.00,17.45)**	(2.00,2.33)	(0.00,0.07)	24.28
EM_{SEL}	(0.40,17.93)	(14.40,25.93)	(42.00,25.63)	**(38.00,14.90)**	(5.00,10.10)	(0.20,5.50)	28.70
EM_{AVG}	(0.00,21.00)	(12.40,24.53)	(44.08,24.55)	**(41.00,18.13)**	(1.80,8.18)	(0.00,3.60)	27.33
DA	(0.00,14.92)	(1.20,22.17)	(31.00,26.08)	**(49.60,21.83)**	(17.20,11.42)	(1.00,3.58)	24.06

Table 13: Simulation study comparing the performance of different designs

From the simulation results, we can see that the four methods each have their own advantages and disadvantages over various working situations. For scenario 1, the most standard design setup, all methods performed similarly well with OD-CRM possessing slight superiority. The latter four scenarios where the target was either by the end or by the beginning of the toxicity set, the OD-CRM and EM-CRM performed relatively stable, as compared to the TITE-CRM. Its performance relied somehow on the skeleton layout, as can be seen from its putting most of the choices on the doses near the fourth one, i.e., the target one in its prior skeleton setup (scenario 2 and 3). We can also sense its conservativeness from its low rate of hit in scenario 3 where the target was the highest dose level, and its high rate of hit in scenario 4 and 5 where the target fell into the lower range of the design set. For scenario 6 where there was a jump between the target dose (the fourth one) and its previous one, all designs had the tendency to compensate for this inconsistency gap of the two consecutive doses by staying at the lower one, as can be seen by the large percentage of selection of the third dose. For scenario 7 where the six toxicity rates were close to each other, all approaches present a not-so-outstanding outcome where the rate of selecting the true MTD was around or below 40%.

We would expect OD-CRM to have slight inferiority comparing with the other three methods for scenario 8, where data were generated solely by power model, the only working model for EM-CRM, TITE-CRM, and DA-CRM, whereas OD-CRM used all three candidates. However, when data were produced by logistic, or probit model alone (scenario 9 and 10), while the OD-CRM still got comparable performances compared to the other three, when examining the percentage of patient treated at each dose level, we found that the OD-CRM put most of the

enrolled patients at the lowest dose, caused by our Bayesian prior choice for model parameter. Therefore, we could see that the OD-CRM, while still yielding satisfying scores, could be more safe in the sense that its dose allocation can operate to place more attention on the lowest one.

We should mention that our approach still got room to improve in terms of its efficacy in selecting the true target dose. More specifically, the real parameter to estimate in the OD-CRM design setup should be x_t, the target dose level that satisfies the following equation,

$$\sum_{m=1}^{3} \pi_m \psi_m(x_t, \theta_m) = p_t \tag{4.7}$$

where same as before, p_t is the target toxicity rate, and (ψ_m, π_m), $m = 1, 2, 3$, are the three candidate models and their weights. Yet, the current parameter to be estimated when implementing the OD-CRM is a weighted version of $x_{1,t}$, $x_{2,t}$, and $x_{3,t}$, where

$$x_{m,t}(\theta_m, p_t) = \psi_m^{-1}(\theta_m, p_t), \quad m = 1, 2, 3.$$

Therefore, for further improvement, we could treat Equation 4.7 as the sole target parameter and take derivatives with respect to θ'_m, then solve for $\dfrac{\partial x_t(\boldsymbol{\theta}, p_t)}{\partial \theta'_m}$, $m = 1, 2, 3$, respectively. By taking this step, the objective function in constructing optimal designs would change from

$$\sum_{m=1}^{3} \pi_m \left[\left(\frac{\partial x_{m,t}(\theta_m, p_t)}{\partial \theta'_m} \right) \mathbf{I}_\xi^{-1}(\theta_m) \left(\frac{\partial x_{m,t}(\theta_m, p_t)}{\partial \theta'_m} \right)' \right]$$

to

$$\sum_{m=1}^{3} \pi_m \left[\left(\frac{\partial x_t(\boldsymbol{\theta}, p_t)}{\partial \theta'_m} \right) \mathbf{I}_{\xi}^{-1}(\theta_m) \left(\frac{\partial x_t(\boldsymbol{\theta}, p_t)}{\partial \theta'_m} \right)' \right],$$

which we believe would enhance the performance of the proposed OD-CRM to a great extent.

CHAPTER 5

CONCLUSIONS AND FUTURE WORK

The main purpose of this dissertation is about improving the efficiency of dose allocation in early-phase clinical trials when the primary endpoint is the toxicity response, and correctly identifying the MTD is the ultimate goal. More specifically, when we take a look at the oncology studies, the target toxicity rate is usually higher than the normal cutoff due to the severeness of the disease, which also often results in an urgent need to find an effective agent with appropriate dose level where the strict requirement of absolute safety could be somewhat loosened. On the other hand, the treatments to tumor/cancer, unlike other general medicines, always incur high level of AEs at the latter half of the usual evaluation period, thus makes the problem of the so-called late-onset toxicities attracting so much attention.

We summarize here in this chapter our primary results on the newly-proposed dose-finding approach, the OD-CRM, where optimal design theory is incorporated into the classic CRM statistical inference framework. We would like to mention that although MTD is the parameter of interest discussed in this thesis, it can be easily extended to other medically significant dose targets, like the MED (minimal effective dose), or the BOD (biological optimal dose), as long as they could be expressed as a function of the assumed working model, i.e., target dose $= b(\theta)$, so that its asymptotic variance could be formulated in terms of the Fisher information matrix, like the one stated in Equation 1.1. Some on-going work and future directions within this area of research are presented in the following sections.

5.1 Conclusions on standard dose-finding problems

OD-CRM applied in a standard MTD-finding problem is introduced in Section 1.2.2 and elaborated in Section 3.1. Its main difference compared with the classic CRM approach lies essentially in the objective function used in choosing the dose level for the next entered cohort of patients. For the classic CRM, in order to obtain d_{next}, we only need to solve for equation $b(\hat{\theta}) = p_t$, where $b(\cdot)$ is the MTD expressed in a form of function of θ, the unknown model parameter, while $\hat{\theta}$ is the latest updated θ estimate, and p_t the target toxicity rate. In comparison, using the asymptotic theory, we minimize the variance of $\widehat{\text{MTD}}$ in order to obtain better estimation accuracy under some optimality criterion, and the corresponding objective function is thus written as $b'(\theta)\mathbf{I}(\theta)b(\theta)$, where $\mathbf{I}(\theta)$ is the Fisher information matrix of parameter θ under the assumed working model $\psi(x, \theta)$.

The conclusions we listed in Section 3.1 provide strong evidence to support the well-admitted claim that the CRM algorithm under standard clinical trial setup, is highly efficient, which has also been demonstrated through many simulation studies (19).

More specifically, we proved that for simple power model, the OD-CRM will always select next dose level with the corresponding toxicity rate very close to 0.2, regardless of the value of the target toxicity rate set in the study. Recall that when CRM was first introduced by O'Quigley et al. in 1990 (40), a toxicity probability of 0.2 was employed as the target rate. Since then, many other studies in related fields also adopt 0.2 as the target toxicity rate to meet standard pharmaceutical requirements. Therefore our optimality result here further confirms their choices of design, which set the target toxicity rate to be 0.2, to be not only medically

reasonable, but also statistically optimal. If the on-going medical trial fixes its p_t to be some value other than 0.2, but stays close, the efficiency loss, from the optimal design perspective, is quite small and can be neglected (Table 6). The result is very encouraging because now we have known that under the simple power model, as long as the target toxicity rate is chosen from a reasonable range (say, from 0.1 to 0.35), the standard CRM procedure will generate an optimal design, or at least a nearly optimal design with negligible efficiency loss. Then the simulations conducted further (Table 8) reinstated our conclusion's liability in the sense that it stands not just under the asymptotic structure, but holds when constrained by limited sample size as well.

As for the case of the two-parameter logistic and probit model, when the target toxicity rate p_t is set to be less than 0.5, under model parameter assumptions (Equation 3.5, Equation 3.12), we proved that the standard CRM algorithm is exactly optimal when MTD is the target dose to be identified, which justifies the efficiency of the CRM theoretically from the optimal design point of view.

We should also mention that Theorems 2 and 3 are not subject to constraint $0 < p_t < 0.5$. In fact, for the case $p_t > 0.5$, as long as parameter α in the model is negative and independent of p_t (as compared to the p_t-involved upper bound stated in Equation 3.5 and Equation 3.12), the range for p_t can be widened to cover almost all the $(0, 1)$ interval (detailed proof not shown here). However, since in a practical clinical trial, it is rare to see the target toxicity rate being set higher than 0.5, we will thus not elaborate more on this circumstance.

5.2 Conclusions on dose-finding problems with delayed-responses

OD-CRM applied in a MTD-finding problem with late-onset toxicities is introduced in Section 1.2.3 and elaborated in Section 3.2. The dose assignment part in the method is still taken care of by the optimal design theory, whereas for the newly arisen delayed-response problem, we address it by attaching different weights to different observations based on their "liability". This "liability" of each data point is associated with their current DLT response, enrollment time, and assigned dose level, then formulated using a conditional probability that links the true toxicity rate with the observed response at each time point. This weighing mechanism essentially incorporates recorded data, whether it is fully-evaluated or not, into the statistical inference procedure in a "down-weighted" manner. This approach prevents over-estimation of the MTD by throwing incomplete data away which could result in a false-optimistic guess of patients' toxic reaction, and at the same time makes use of all the statistics at hand to generate more informative estimates, both for the unknown parameters and the underlying working model, therefore is deemed particularly capable in terms of shortening the trial duration to a great extent.

The result we presented in Theorem 5 provides us with a general guidance of dose selection when we assume the simple power model as the only working model. As the conditions become complicated with the increase of parameter dimension, Theorem 7 and 9 give the optimal dose allocation under D-optimality for the first stage of a MTD-finding trial, under the two-parameter logistic and probit model, respectively. Then in terms of a broader clinical setup with multi-stage designs and multiple working models, we offer a general dose-finding algorithm

which is built on the foundation of an efficient and well-established optimal-design-construction algorithm, i.e., the OWEA (56).

We compare the OD-CRM with three other designs that are widely implemented in the late-onset toxicity realm, namely, the TITE-CRM (8), the EM-CRM (59), and the DA-CRM (32). The TITE-CRM is one of the most early proposed method dealing with the problem, and it is the first design that came up with the weighing mechanism we mentioned and also used in our method. The latter two approaches treat the delayed responses as missing data, and utilize either a modified EM algorithm, or the Bayesian data augmentation technique, to substitute the incomplete observations with their "best guess" of toxicity outcome.

Empirical studies were conducted under eleven toxicity configurations to cover various dose-response scenarios. BMA framework was employed in the OD-CRM designs to compensate for the uncertainty of the underlying working system. The update of the weight function was done also under Bayesian structure where for each interim study time point, a Beta prior was assumed and conjugated with the Binomial toxicity data. Simulation results, as tabulated in Table 13, show great potential of the OD-CRM, as its ability to remain stable in terms of its performance of identifying the true MTD (percentage ranges from about 30% to 70%), under so many dissimilar scenarios, which includes a non-parametric case (scenario 11) where the toxicity data were not generated by any parametric model.

Moreover, as we can see from the first two, three columns of the table, under the OD-CRM designs, almost all patients (up to 90%) were administered with the lowest two, three doses; and the total DLT occurrence rates (the last column) were controlled under a reasonable

bound (35%), even for the case with a high-toxicity generator (scenario 5). This is a very appealing property for safety and ethical concerns that researchers and practitioners may have with respect to this method.

One more thing we should point out is the flexibility of our method. The dose-finding algorithm we offer here can easily be modified to embrace multiple targets. For example, if we want to estimate MTD and MED at the same time, an easy and natural way of doing so would be to change the objective function from $\hat{\mathbf{V}}(\widehat{\text{MTD}})$ to $\frac{1}{2}\hat{\mathbf{V}}(\widehat{\text{MTD}}) + \frac{1}{2}\hat{\mathbf{V}}(\widehat{\text{MED}})$, which could be rather difficult for the other non-variance based designs, since their way of dose selection is through solving an objective equation, and an objective equation system corresponding to multiple targets would result in multiple solutions thus rendering the following dose allocation process tricky and complex.

5.3 Future work

Some of the very interesting and worth-exploring problems are roughly discussed here in this section.

1. Different weighting mechanism.

   Although we practiced the combination of optimal design and Cheung and Chappell's weight function, some other weighting mechanism could also be incorporated into our OD-CRM design framework. For example, based on the interpretation of weight function embedded in the time-to-toxicity regression model (Equation 2.3), we should have $w_i(u, T) = \dfrac{H_i(u)}{\psi(d_i, \theta)}$, where $H_i(u)$ is the time-to-toxicity distribution under dose i. Thus

following two popular $H_i(u)$ assumptions, we could utilize the following two formulas to estimate each w_i.

- When time-to-toxicity U follows a log-logistic model with scale parameter 1 and location parameter b_i.

$$w_i(u,T) = \frac{H_i(u)}{\psi(d_i,\theta)} = \frac{\frac{1}{1+u^{-b_i}}}{p_i} = \frac{1}{p_i\left(1+u^{\log_T(\frac{1}{p_i}-1)}\right)}.$$

  The last equality stems from the constraint that the location parameter b_i's should be chosen so that the distribution of U_i at $u = T$ (the end of the evaluation period) would equal to its corresponding toxicity probability, i.e., $H_i(T) = p_i$.

- When time-to-toxicity U follows a Weibull model with shape parameter 4 and scale parameter λ_i.

$$w_i(u,T) = \frac{H_i(u)}{\psi(d_i,\theta)} = \frac{1-\exp\left(-\left(\frac{u}{\lambda_i}\right)^4\right)}{p_i} = \frac{1}{p_i}\left\{1-\exp\left[-\frac{u^4}{T^4}\left(\log\frac{1}{1-p_i}\right)\right]\right\}.$$

  λ_i's are to be chosen in similar fashion as described in the log-logistic model case.

Therefore, the $w_i(u,T)$ is estimated at each stage with p_i replaced by $\psi(d_i,\hat{\theta})$. Notice that here the weight function is updated under a heterogeneous structure such that patients with different dose administrations, d_i and d_j, $i \neq j$, will be assigned different weights to their observations, regardless of whether they have been enrolled for the same duration of time or not.

2. Adding some randomness into the design.

   One may argue that many good properties of the optimal design theory lie within a continuous data universe. Although in our proposed algorithm, optimal dose(s) is/are chosen from the available dose set so that dose assignment could be followed directly, a stronger result could be generated when we have a continuous dose range to construct optimal designs from, which, in a practical situation, is often unattainable. Therefore, further investigation on new types of design (e.g., add some random mechanism into the sampling procedure) could be helpful in order to balance the goal of achieving certain optimality criterion and obtaining consistency for parameter estimation in dose-finding problems, when only few dose levels are available at each recruitment stage.

   For example, the EM-CRM provides us with a very attractive data-manipulating strategy. In future work, instead of bringing the weighted version of the data into the model, we could consider substituting each delayed toxicity with its predicted risk obtained by reiterating its expectation based on the parameter estimates and the parameter updates based on the"upgraded" data. Then at the end of each iteration, the converged Marcov chain would yield a final $\hat{\theta}$ and $\mathbf{E}(\mathcal{Y})$, which are then built into the Fisher information and likelihood function to guide the following optimal-dose(s) finding process.

3. Dose combination.

   Dual-agent problem is also one of the most intriguing problems encounted in dose-finding studies. The interaction of the two drugs may put the dose-toxicity monotonicity into a questionable place. One of the method to address this problem would be a partial-order

(PO) design, meaning that there exists only a few pairs of treatments whose ordering of the toxicity probabilities are known at the beginning of the trial. Then several guesses would be proposed regarding the rest of the toxicity probabilities, with each guess representing a unique model, thus rendering the dose-combination problem into a model averaging or model selection problem. A TITE design combined with this PO structure was discussed in Wages, Conaway, and O'Quigley (54).

The DA-CRM approach (32) we discussed in earlier chapters can also be extended to embrace this dual-agent problem. Liu and Ning (31) proposed this modification of the DA-CRM by modeling the two-dimensional dose-toxicity surface using the Finney model (18), which is broadly applied in drug-to-drug interaction studies (22).

4. Involving efficacy outcome.

   Another practical impediment in adaptive clinical trials is the difficulty in a fully-usage of the collected data. Usually the data accrued in Phase I studies are only examined for the toxicity responses but not the efficacy. One reason would be that the subject pool for early-phase studies only involves healthy volunteers while efficacious effect is normally seen on patients with the target disease. However, the oncology trials possess this advantage of recruiting patients with actual tumor/cancer even at Phase I (because the toxic effect of an anti-tumor drug on a healthy person would be too much to withhold). Therefore we could consider a streamline of Phase I/II design where toxicity and efficacy are modeled at the same time.

Specifically, we consider grouping the binary bivariate responses into ordinal outcomes, say, no DLT and no efficacy would be the 1st category, no DLT and efficacy would be the 2nd, and DLT the 3rd. Then by utilizing a proportional odds model, or a continuation ratio model, these three outcomes would be seen as a realization from a multinomial distribution with each probability expressed out according to the chosen model. We also would like to extend this line of thought into the dual-agent complication which would enlarge the parameter dimension to four (proportional odds model) and six (continuation ratio model). It still requires substantial additional work to get obtain an organized framework. We will continue exploring this path with the hope of developing a novel and practical solution.

CHAPTER 6

APPENDIX

Declaration: Part of this dissertation was published in two of the author's publications: (52) and (53). Copyright permission has been attained from corresponding publishing companies: Elsevier (for Statistics & Probability Letters), and Taylor & Francis (for Journal of Statistical Theory and Practice). Permission files are attached here for reference.

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CITED LITERATURE

1. Ahn, C.: An evaluation of phase i cancer clinical trial designs. Statistics in medicine, 17(14):1537–1549, July 1998.

2. Babb, J., Rogatko, A., and Zacks, S.: Cancer phase i clinical trials: efficient dose escalation with overdose control. Statistics in medicine, 17(10):1103–1120, May 1999.

3. Bekele, B. N. e. a.: Monitoring late-onset toxicities in phase i trials using predicted risks. Biostatistics, 9(3):442–457, July 2008.

4. Biedermann, S. and Woods, D. C.: Optimal designs for generalized nonlinear models with application to secondharmonic generation experiments. Journal of the Royal Statistical Society: Series C (Applied Statistics), 60(2):281–299, March 2011.

5. Braun, T. M.: Generalizing the titecrm to adapt for earlyand lateonset toxicities. Statistics in medicine, 25(12):2071–2083, June 2006.

6. Buckland, S. T., Burnham, K. P., and Augustin, N. H.: Model selection: an integral part of inference. Biometrics, 53(2):603–618, June 1997.

7. Chaloner, K. and Verdinelli, I.: Bayesian experimental design: A review. Statistical Science, 10(3):273–304, August 1995.

8. Cheung, Y. K. and Chappell, R.: Sequential designs for phase i clinical trials with lateonset toxicities. Biometrics, 56(4):1177–1182, December 2000.

9. Cheung, Y. K. and Chappell, R.: A simple technique to evaluate model sensitivity in the continual reassessment method. Biometrics, 58(3):671–674, September 2002.

10. Chu, P.-L., Lin, Y., and Shih, W. J.: Unifying crm and ewoc designs for phase i cancer clinical trials. Journal of Statistical Planning and Inference, 139(3):1146–1163, March 2009.

11. Coia, L. R., Myerson, R. J., and Tepper, J. E.: Late effects of radiation therapy on the gastrointestinal tract. International Journal of Radiation Oncology Biology Physics, 31(5):1213–1236, March 1995.

12. Cooper, J. S. e. a.: Late effects of radiation therapy in the head and neck region. International Journal of Radiation Oncology Biology Physics, 31(5):1141–1164, March 1995.

13. Crowley, J. and Hoering, A.: Handbook of statistics in clinical oncology. Chapman and Hall/CRC, 2012.

14. Dempster, A. P., Laird, N. M., and Rubin, D. B.: Maximum likelihood from incomplete data via the em algorithm. Journal of the royal statistical society. Series B (methodological), 39(1):1–38, January 1977.

15. Durham, S. D. and Flournoy, N.: Random walks for quantile estimation. Statistical decision theory and related topics V, pages 467–476, December 1994.

16. Durham, S. D., Flournoy, N., and Rosenberger, W. F.: A random walk rule for phase i clinical trials. The annals of applied statistics, 53(2):745–760, June 1997.

17. Elfving, G.: Optimum allocation in linear regression theory. The Annals of Mathematical Statistics, 13(2):255–262, 1952.

18. Finney, E. E.: Dynamic elastic properties and sensory quality of apple fruit. Journal of texture studies, 2(1):62–74, January 1971.

19. Garrett-Mayer, E.: The continual reassessment method for dose-finding studies: a tutorial. Clinical Trials, 3(1):57–71, February 2006.

20. Gelfand, A. E. and Ghosh, S. K.: Model choice: a minimum posterior predictive loss approach. Biometrika, 85(1):1–11, March 1998.

21. Goodman, S. N., Zahurak, M. L., and Piantadosi, S.: Some practical improvements in the continual reassessment method for phase i studies. Statistics in medicine, 14(11):1149–1161, June 1995.

22. Greco, W. R., Bravo, G., and Parsons, J. C.: The search for synergy: a critical review from a response surface perspective. Pharmacological reviews, 47(2):331–385, June 1995.

23. Hjort, N. L. and Claeskens, G.: Frequentist model average estimators. Journal of the American Statistical Association, 98(464):879–899, December 2003.

24. Hodgson, D. C.: Long-term toxicity of chemotherapy and radiotherapy in lymphoma survivors: optimizing treatment for individual patients. Clinical advances in hematology & oncology, 13(2):103–12, February 2015.

25. Hoeting, J. A. e. a.: Bayesian model averaging: a tutorial. Statistical science, 14(4):382–401, November 1999.

26. Ji, Y. and Bekele, B. N.: Adaptive randomization for multiarm comparative clinical trials based on joint efficacy/toxicity outcomes. Biometrics, 65(3):876–884, September 2009.

27. Kaplan, E. L. and Meier, P.: Nonparametric estimation from incomplete observations. Journal of the American statistical association, 52(282):457–481, June 1958.

28. Kiefer, J.: General equivalence theory for optimum designs (approximate theory). The Annals of Statistics, 2(5):849–879, September 1974.

29. Korn, E. L. e. a.: A comparison of two phase i trial designs. Statistics in medicine, 13(18):1799–1806, September 1994.

30. Lee, S. M. and Cheung, Y. K.: Model calibration in the continual reassessment method. Clinical Trials, 6(3):227–238, June 2009.

31. Liu, S. and Ning, J.: A bayesian dose-finding design for drug combination trials with delayed toxicities. Bayesian analysis, 8(3):703, September 2013.

32. Liu, S., Yin, G., and Yuan, Y.: Bayesian data augmentation dose finding with continual reassessment method and delayed toxicity. The Annals of Applied Statistics, 7(4):1837, December 2013.

33. Madigan, D. and Raftery, A. E.: Model selection and accounting for model uncertainty in graphical models using occam's window. Journal of the American Statistical Association, 89(428):1535–1546, December 1994.

34. Mller, S.: An extension of the continual reassessment methods using a preliminary up-and-down design in a dose finding study in cancer patients, in order to investigate a greater range of doses. Statistics in medicine, 14(9):911–922, May 1995.

35. Muler, J. H. e. a.: Phase i trial using a time-to-event continual reassessment strategy for dose escalation of cisplatin combined with gemcitabine and radiation therapy in pancreatic cancer. Journal of Clinical Oncology, 22(2):238–243, January 2004.

36. Nie, L. e. a.: Rendering the 3+ 3 design to rest: more efficient approaches to oncology dose-finding trials in the era of targeted therapy. pages 2623–2629, 2016.

37. O'Quigley, J.: Another look at two phase i clinical trial designs. Statistics in medicine, 18(20):2683–2690, October 1999.

38. O'Quigley, J.: Theoretical study of the continual reassessment method. Journal of Statistical Planning and Inference, 136(6):1765–1780, June 2006.

39. O'Quigley, J. and Chevret, S.: Methods for dose finding studies in cancer clinical trials: a review and results of a monte carlo study. Statistics in medicine, 10(11):1647–1664, November 1991.

40. O'Quigley, J., Pepe, M., and Fisher, L.: Continual reassessment method: a practical design for phase 1 clinical trials in cancer. Biometrics, 46(1):33–48, March 1990.

41. O'Quigley, J. and Shen, L. Z.: Continual reassessment method: a likelihood approach. Biometrics, 52(2):673–684, June 1996.

42. Postel-Vinay, S. e. a.: Phase i trials of molecularly targeted agents: should we pay more attention to late toxicities? Journal of Clinical Oncology, 29(13):1728–1735, March 2011.

43. Reiner, E., Paoletti, X., and O'Quigley, J.: Operating characteristics of the standard phase i clinical trial design. Computational Statistics & Data Analysis, 30(3):303–315, May 1999.

44. Sampford, M. R.: The estimation of response-time distributions. i. fundamental concepts and general methods. Biometrics, 8(1):13–32, March 1952.

45. Sampford, M. R.: The estimation of response-time distributions. ii. multi-stimulus distributions. Biometrics, 8(4):307–369, December 1952.

46. Searle, S. R. and Gruber, M. H.: Linear models.. John Wiley & Sons, 2016.

47. Sherrod, A. M., Brufsky, A., and Puhalla, S.: A case of late-onset gemcitabine lung toxicity. Clinical Medicine Insights. Oncology, 5:171, January 2011.

48. Storer, B. E.: Design and analysis of phase i clinical trials. Biometrics, 45(3):925–937, September 1989.

49. Storer, B. E.: Small-sample confidence sets for the mtd in a phase i clinical trial. The annals of applied statistics, 49(4):1117–1125, December 1993.

50. Storer, B. E.: An evaluation of phase i clinical trial designs in the continuous doseresponse setting. Statistics in medicine, 20(16):2399–2408, August 2001.

51. Tanner, M. A. and Wong, W. H.: The calculation of posterior distributions by data augmentation. Journal of the American statistical Association, 82(398):528–540, June 1987.

52. Tian, T.: A note on continual reassessment method. Statistics & Probability Letters, 113(C):94–102, June 2016.

53. Tian, T. and Yang, M.: Efficiency of the coordinate-exchange algorithm in constructing exact optimal discrete choice experiments. Journal of Statistical Theory and Practice, 11(2):254–268, April 2017.

54. Wages, N. A., Conaway, M. R., and O'Quigley, J.: Using the timetoevent continual reassessment method in the presence of partial orders. Statistics in medicine, 32(1):131–141, January 2013.

55. Yang, M.: On the de la garza phenomenon. The Annals of Statistics, 38(4):2499–2524, 2010.

56. Yang, M., Biedermann, S., and Tang, E.: On optimal designs for nonlinear models: a general and efficient algorithm. Journal of the American Statistical Association, 108(504):1411–1420, December 2013.

57. Yang, M. and Stufken, J.: Support points of locally optimal designs for nonlinear models with two parameters. The Annals of Statistics, 37(1):518–541, February 2009.

58. Yin, G. and Yuan, Y.: Bayesian model averaging continual reassessment method in phase i clinical trials. Journal of the American Statistical Association, 104(487):954–968, September 2009.

59. Yuan, Y. and Yin, G.: Robust em continual reassessment method in oncology dose finding. Journal of the American Statistical Association, 106(495):818–831, September 2011.

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KEY SKILLS

- Optimal Design Theory
- Phase I/II clinical trials
- Optimal Design Algorithm
- Bayesian Adaptive Design

EDUCATION

Nankai University, China **2008 – 2012**
Department of Mathematics
-- Statistics major with an average score of 86.2/100 in all mathematical courses and 87.6/100 in all statistical courses;

University of Illinois at Chicago, USA **2012 – 2017**
Department of Mathematics, Statistics and Computer Science
-- Ph.D. graduate from the statistics program with a 4.0 GPA;
-- Earned a Master Degree in statistics in spring, 2013 with a perfect master exam credit of 160/160.

RELATED EXPERIENCES

RESEARCH ASSISTANT **MSCS, UIC; 2014 – 2017**
Research is mainly focused on phase I/II clinical trials. More specifically, to incorporate optimal design theory into current dose-finding problems with the goal of making efficient allocations of testing agents.

STUDENT INTERN **CDER, FDA; May 2015 – 2017**
Three research projects are being carried out:

1. **Designs in dose-finding problems with late-onset toxicities**
- Pseudo responses are introduced and incorporated into building dose-toxicity models;
- Primary goal is to accurately identify any quantity of interest (e.g., MTD) with the help of making use of "incomplete" data to precede any ongoing trials presented with delayed responses.

2. **Optimal exposure in oncology studies with targeted occupancy rate**
- Beta-distributed PD data with Emax occupancy model are studied;
- Primary goal is to derive corresponding exposure value(s) with a given occupancy rate

3. **Optimal dual-agent allocations in Phase I/II clinical trials using ordinal outcomes**
- Both proportional odds (PO) model and continuous ratio (CR) model extended with double doses are explored;
- Primary goal is to find biologically optimal doses (BODs) through optimal design theory.

PUBLICATIONS

1. Tian Tian, A Note on Continual Reassessment Method, *Statistics and Probability Letters* (2016), 113, pp. 94-102.
2. Tian Tian, Min Yang, Efficiency of the Coordinate-Exchange Algorithm in Constructing Exact Optimal Discrete Choice Experiments, *Journal of Statistical Theory and Practice* (2017), 11(2), pp. 254-268.

PRESENTATIONS

1. Estimation Efficiency in Continual Reassessment Method

- Statistics seminar, University of Illinois at Chicago, Feb. 2015.
- Poster session, Midwest Biopharmaceutical Statistics Workshop, May 2015.

2. Optimal Design Theory in Phase I Clinical Trials

- Departmental talk, The Institute of Statistics at Nankai University, Dec. 2015 (***invited***).
- International Conference on Design of Experiments (ICODOE), University of Memphis, May 2016.

3. A Discussion on the Performance of the Coordinate-Exchange Algorithm

- Graduate statistics seminar, University of Illinois at Chicago, Feb. 2016.

4. Optimal Subsampling under Logistic Regression Model

- Student showcase, Chicago Chapter of the American Statistical Association, Mar. 2016 (***selected and awarded***).

5. Optimal Designs in Early-phase Dose-Finding Studies with Late-onset Toxicities

- FDA, CDER, DBV Staff meeting, July, 2016.
- Biopharmaceutical Section, Joint Statistical Meetings (JSM), Chicago, Aug. 2016 (***invited***).
- Graduate statistics seminar, University of Illinois at Chicago, Nov. 2016.
- Poster session, NIC-ASA and ICSA Midwest 2016 Joint Fall meeting, Nov. 2016.
- The 2nd Symposium on Early Phase Trial Design Methodology, UVA, Apr. 2017 (***invited***).

6. Intuitive thinking in optimal design theory

- Graduate statistics seminar, University of Illinois at Chicago, Sept. 2016.

CONSULTING PROJECTS

1. The Commonly Used Anesthetic Propofol Increases Host Susceptibility to Microbial Infection (Manuscript), Department of Microbiology and Immunology, UIC, 2014
- To validate/recommend statistical methods used in data analysis and write a statistical method report for the manuscript.

2. Is Gentrification the New Restrictive Covenant: Choice in Changing Neighborhood? Department of Urban Planning and Policy, UIC, 2015
- To build models and test the degree to which changes in social and economic diversity affects gentrification; and then to compare the change in covariate significance across the selected periods;
- To write a statistical analysis report.

3. Today's Youth, Tomorrow's Leaders? Asian American Studies Department, UIC, 2016
- To study changes in civic and political engagement aspirations across immigrant generations using general ordered logit regression.

MANUSCRIPT REVIEWS

Annals of Statistics, Journal of the American Statistical Association, Journal of Statistical Theory and Practice, Kwait Journal of Science, Statistical Science, Statistica Sinica, Statistics and Probability Letter.

REFEREES

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